PSYCHOLOGICAL RECOVERY AFTER MILD TRAUMATIC BRAIN INJURY: EVALUATING DIAGNOSTIC APPROACHES AND RETURN TO WORK

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The more I learn,
the more I realize,
how much I don't know.

Albert Einstein

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ABSTRACT

Mild traumatic brain injury (mTBI) is one of the most common neurological disorders diagnosed in emergency departments. The first steps towards successful trauma management are accurate injury diagnosis, followed by guidelines for everyday life post-injury, such as recommendations on when to return to work.

The present cumulative PhD thesis has the following main goals: (1) to evaluate diagnostic approaches to predict cognitive outcome and persistent post-concussion symptoms (pPCS), and (2) to investigate the beneficial time to return to work after mTBI. Based on the conclusions of a literature review (paper 1) two newer MRI-techniques, the so called susceptibility weighted imaging (SWI) and diffusion tensor imaging (DTI) methods, were chosen as diagnostic measures to predict cognitive outcome and pPCS in a sample of patients sustaining mTBI followed-up during one year (paper 2). To gain more knowledge about the possible influence of time until return to work on cognitive recovery and pPCS after mTBI, the participants were randomly allocated a recommendation of three or seven days until return to work and their effective time until return to work was measured (paper 3). According to the results, SWI seems to be an appropriate measure to detect microbleeds (MB) that could be considered as a prognostic factor for cognitive outcome and pPCS after mTBI. Patients with a recommendation to return to work after three days showed worse outcome regarding posttraumatic symptoms, yet better performance in several neuropsychological test scores than the group, which received a recommendation to return to work after seven days. Further analyses revealed that the group with an absolute return to work within one week resumed with a higher workload, showed lower symptom severity in fatigue at three and twelve months, less clinical signs of post-concussion syndrome (PCS) and faster performance in fine motor speed at twelve months, than the group returning to work after one week.

The findings are discussed against the background of current knowledge about MB in mTBI and post-injury recommendations such as return to work. Implications for the clinical management of mTBI patients are derived and recommendations for further studies are made.

ZUSAMMENFASSUNG

Das leichte Schädelhirntrauma (lSHT) ist eine der häufigsten diagnostizierten neurologischen Störungen auf der Notfallstation. Die ersten Schritte zu einer erfolgreichen Behandlung sind die korrekte Diagnose, gefolgt von Leitlinien für den Alltag nach der Verletzung, wie z.B. Empfehlungen für die Rückkehr zur Arbeit.

Die vorliegende kumulative Dissertation hat die folgenden Hauptziele: (1) die Evaluierung diagnostischer Methoden zur Vorhersage kognitiver Folgen und persistierender postkontusioneller Symptome (englische Abkürzung: pPCS) sowie (2) die Untersuchung der erforderlichen Zeit bis zur Rückkehr zur Arbeit nach lSHT. Basierend auf den Schlussfolgerungen einer Literaturarbeit (Artikel 1) wurden zwei neuere Magnetresonanztomographie (MRT)-Techniken, die sogenannte suszeptibilitätsgewichtete Bildgebung (englische Abkürzung: SWI) und Diffusions-Tensor-Bildgebung (englische Abkürzung: DTI), ausgewählt als diagnostische Messinstrumente zur Vorhersage kognitiver Folgen und pPCS in einer Stichprobe von Patienten mit lSHT, welche während einem Jahr nachbetreut wurden (Artikel 2). Um mehr Wissen über den möglichen Einfluss der Zeit bis zur Rückkehr zur Arbeit auf die kognitive Genesung und pPCS nach einem lSHT zu gewinnen, erhielten die Studienteilnehmer eine Empfehlung für drei oder sieben Tage bis zur Rückkehr zur Arbeit zufällig zugeteilt und die effektive Zeit bis zur Rückkehr zur Arbeit wurde erfasst (Artikel 3). Gemäss den Resultaten scheint die SWI-Methode ein geeignetes Messverfahren für die Entdeckung von Mikroblutungen zu sein, welche als ein Prognosefaktor für den kognitiven Verlauf und pPCS nach einem lSHT erachtet werden könnten. Patienten mit einer Empfehlung nach drei Tagen zur Arbeit zurückzukehren zeigten einen schlechteren Verlauf im Hinblick auf pPCS, hingegen bessere Leistungen in mehreren neuropsychologischen Testwerten im Vergleich zur Gruppe, welche eine Empfehlung für sieben Tage bis zur Rückkehr zur Arbeit erhalten hatte. Weitere Auswertungen zeigten, dass die Gruppe mit einer effektiven Rückkehr zur Arbeit innert einer Woche mit höherem Arbeitspensum einstieg, tiefere Werte im Symptom „Fatigue“ nach drei und zwölf Monaten, weniger klinische Hinweise für ein postkontusionelles Syndrom und eine schnellere Leistung in der feinmotorischen Geschwindigkeit nach zwölf Monaten zeigte, als die Gruppe mit Rückkehr zur Arbeit nach einer Woche.

Die Erkenntnisse werden vor dem Hintergrund von aktuellem Wissen über Mikroblutungen bei lSHT und über Empfehlungen nach der Hirnverletzung diskutiert, z.B. hinsichtlich empfohlener Rückkehr zur Arbeit. Für die klinische Behandlung von lSHT Patienten werden Schlussfolgerungen abgeleitet und es werden Empfehlungen für weitere Studien gemacht.

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ABBREVIATIONS

AD	Axial Diffusivity
ADL	Activities of Daily Living
CT	Computer Tomography
CTRL	Healthy Controls
DAI	Diffuse Axonal Injury
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
GOS	Glasgow Outcome Scale
FA	Fractional Anisotropy
FUP	Follow-up
fMRI	functional Magnetic Resonance Imaging
GCS	Glasgow Coma Scale
ICD	International Classification of Disease
ImPACT	Immediate Post-Concussion and Cognitive Testing
LOC	Loss of Consciousness
MB	Microbleeds
MD	Mean Diffusivity
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
mTBI	mild Traumatic Brain Injury
PCS	Post-Concussion Syndrome
PCSS	Post Concussion Symptom Score
pPCS	persistent Post-Concussion Symptoms
pPTS	persistent Post-Traumatic Symptoms
PTA	Posttraumatic Amnesia
PTSD	Post-Traumatic Stress Disorder
RD	Radial Diffusivity
ROI	Region of interest
RTW	Return-To-Work
SWI	Susceptibility Weighted Imaging
TBI	Traumatic Brain Injury
TBSS	Tract-Based Spacial Statistics
VBM	Voxel-Based Morphometry

1. INTRODUCTION

The incidence of mild traumatic brain injury (mTBI) is between 100 and 400 per 100'000 individuals per year in developed countries (Styrke, Stålnacke, Sojka, & Björnstig, 2007). According to the Swiss accident insurance 300 to 400 per 100'000 individuals experience a mTBI per year in Switzerland. The incidence of mTBI may actually be under-reported, because many patients never seek medical attention unless the symptoms worsen or persist. Most patients recover from a single mTBI within weeks to months without specific treatment. Despite this, the long-term prevalence for persistent physical, cognitive and/or emotional posttraumatic symptoms, also known as Post-Concussion Syndrome (PCS), is estimated between 15 and 30% (Hou et al., 2012). Currently, no sensitive diagnostic methods for prognostication of persistent post-concussion symptoms (pPCS) or cognitive deficits exist, nor do evidence-based recommendations regarding the most beneficial time of sick leave after a mTBI.

The present PhD thesis focuses on the evaluation of diagnostic approaches to predict pPCS and on beneficial time to return to work after mTBI. The thesis begins with an introduction to mTBI, its pathophysiology and PCS, followed by an overview of diagnostic approaches used to predict outcome in mTBI, the current state of the art regarding clinical management and sick leave, respectively return to work (chapter 1). Based on this current knowledge, research questions of the current PhD-project are specified and these questions are addressed in the subsequent three publications, the first being a literature review on diagnostic approaches to predict outcome after mTBI, the second and third being original research articles about the results of the current empirical study (chapter 2). Finally, the results and rationale of these three papers are integrated in a general discussion, which states implications for clinical practice and future research (chapter 3).

1.1. Definition of terms and current knowledge

1.1.1. Mild traumatic brain injury – definition and epidemiology

The diagnosis of mTBI historically has been very challenging, on one hand due to the continuing debate over the clinical definition (Bigler, 2008) and on the other hand because of the dependency on patient's subjective self-report about the acute characteristics of their injury (Maruta, Lee, Jacobs, & Ghajar, 2010). The self-report of deficits may be falsified by the patient's reduced awareness of deficits due to cognitive impairment. Patients with mTBI have by definition very subtle changes in mental status, and fewer than 10% result in an initial loss

of consciousness (Wright, 2008). The World Health Organization defined mTBI as follows (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004): "MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include:

A) One or more of the following: confusion or disorientation, loss of consciousness (LOC) for 30 minutes or less, post-traumatic amnesia (PTA) for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure and intracranial lesions not requiring surgery;
B) Glasgow Coma Scale (GCS) score of 13 to 15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of mTBI must not be due to drugs, alcohol and medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating cranio-cerebral injury."

The process of diagnosing patients with mTBI is complicated by missing information about the course of events of the accident, extracranial injuries and frequent co-occurrence with alcohol. Currently, there is no widely available and reliable test that can confidently confirm or rule out the presence of a mTBI. Several symptoms, signs and risk factors associated with an increased risk of intracranial injury have been identified (Vos et al., 2002). These factors include unclear or ambiguous accident history, continued PTA, retrograde amnesia longer than 30 min, trauma above the clavicles including clinical signs of skull fracture, severe headache, vomiting, focal neurological deficit, seizure, age < 2 years, age > 65 years, coagulation disorders, high-energy accident or intoxication with alcohol/drugs. On the other hand, a Task Force on mTBI of the European Federation of Neurological Societies declared mTBI is ruled out and called only "head injury" if a patient presents with GCS of 15 and neither LOC, PTA nor risk factors associated with an increased risk of intracranial injury (Vos et al., 2002).

1.1.2. Pathophysiology of mild traumatic brain injury

Traumatic brain injury is not only caused by a direct impact to the head by an external mechanical force, but also by sudden acceleration, deceleration or rotation, leading to stretching and twisting of axons followed by metabolic and mechanical changes (Bazarian, Blyth, & Cimpello, 2006; Iverson, 2005). The underlying pathophysiology for mTBI is not as clear as that of moderate and severe TBI. A leading hypothesis is, that the biomechanical force of a

mTBI results in a neurometabolic cascade, leading to a predominantly functional disorganisation on cellular level including ionic fluxes, an energy crises due to increased energy consumption devoted to neural repair and return to homeostasis, while there is less energy available and neurotransmission such as indiscriminate glutamate release is impaired (Giza & Hovda, 2001, 2014). The biomechanical stretch force of a mTBI is also associated with microstructural damage, for which the axons are said to be especially vulnerable. Links between the pathophysiology after mTBI and clinical symptoms respectively cognitive impairment have been proposed, e.g. the ionic flux is proposed to lead to migraine headache, photophobia and phonophobia. Diffuse axonal injury (DAI) and impaired neurotransmission are said to lead to transient deficits in cognitive performance in domains such as processing speed, working memory and attention (Wallesch et al., 2001).

The brain may be exceedingly vulnerable, especially during the first ten days post-injury while the cellular energy crises is ongoing and when challenged, e.g. by low oxygen state, recurrent insult or concussion, could produce an exponential increase in dysfunction and cellular injury. In fact, anything that increases metabolic demand, such as heavy mental or physical exercise, could aggravate the injury (Wright, 2008). Even months to years after mTBI areas of focal cortical dysfunction in conjunction with blood-brain barrier disruption and reduced regional cerebral blood flow were shown in Single Photon Emission Computed Tomography (SPECT) (Korn, Golan, Melamed, Pascual-Marqui, & Friedman, 2005). This is suggestive of long-term altered brain metabolism.

1.1.3. Post-concussion syndrome (PCS)

Some patients experience a set of cognitive difficulties involving memory, attention and executive functioning, persisting physical complaints like headache and fatigue and/or psychiatric symptoms like anxiety or depression, often referred to as Post-Concussion Syndrome (PCS) beyond the acute phase post-injury (Ryan & Warden, 2003). The estimated prevalence of PCS varies widely, mostly due to varying diagnostic criteria and time of evaluation post-injury, with an estimated 15 to 30% reporting symptoms beyond 3 months (Hou et al., 2012) and at least 10% at 1 year (von Wild, K R H, 2008). A study comparing the prevalence and specificity of diagnostic criteria for PCS between the International Classification of Disease, Tenth Revision (ICD-10; WHO, 1992) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) three month after injury found that prevalence of PCS was higher using ICD-10 (64%) than DSM-IV criteria (11%;

(Boake et al., 2005). The diagnostic criteria for PCS according to Code F07.2 of ICD-10 (WHO, 1992) are:

A) a syndrome that occurs following head trauma (usually sufficiently severe to result in loss of consciousness) and
B) the presence of three or more of the following eight symptoms:
   1) Headache, 2) dizziness, 3) fatigue, 4) irritability, 5) insomnia, 6) concentration difficulty, 7) memory difficulty, 8) intolerance of stress, emotion or alcohol.

The diagnostic criteria for postconcussional disorder (PCD) of DSM-IV (American Psychiatric Association, 1994) are:

A) history of TBI causing "significant cerebral concussion";
B) cognitive deficit in attention and/or memory;
C) presence of at least three of eight symptoms (e.g. fatigue, sleep, disturbance, headache, dizziness, irritability, affective disturbance, personality change and/or apathy) that appear after injury and persist for three months;
D) symptoms that begin or worsen after injury;
E) interference with social role functioning; and
F) exclusion of dementia due to head trauma and other disorders that better account for the symptoms.

Since the Cantonal Hospital of St.Gallen, where the data of the current PhD-project were collected, relies on the ICD-10 criteria for the diagnosis of PCS, we used these criteria for the two original studies (paper 2 and 3). At the same time, some of the additional criteria of DSM-IV (B, D, E, F) are likely to be accounted for in daily clinical practice when it comes to the decision if a patient will receive further treatment by a neuropsychologist since personal resources are limited.

Concerns of defining a syndrome by symptoms that have a high prevalence in the general population or in other syndromes exist. There is an ongoing debate what causes PCS in some mTBI patients while others fully recover within days to weeks. Some established risk factors for the development of PCS are a history of previous head injury, neurological or psychiatric problems, expectations of disability, to be a student, female gender, older age and motor vehicle accidents as cause of injury (Ponsford et al., 2000; Ryan & Warden, 2003). It seems most

probable that PCS can be explained best by a biopsychosocial model including a combination of physiological, psychological and social factors present before, during and after injury.

To differentiate between PCS as defined by the above criteria of ICD-10 and single persistent symptoms occurring after mTBI we initially chose the term “persistent posttraumatic symptoms” and used it in the review paper. Due to the critic that this term is more likely to be associated with the Post-Traumatic Stress Disorder (PTSD) - which might occur in mTBI, but is not the content of this study - than with mTBI, we changed to the term „persistent post-concussion symptoms“ (pPCS) to refer to single persistent symptoms occurring after a mTBI and which do not necessarily fulfill ICD-10 criteria of PCS.

1.1.4. Diagnostic approaches to predict outcome after mTBI

A diagnostic approach that would allow identification of patients who might continue to have persistent symptoms after mTBI, which struggle to return to work and should therefore be offered early treatment, would markedly improve injury management in clinical practice. Especially since some past studies have suggested that earlier intervention is more likely to improve outcome (King, 2003); (Ponsford et al., 2002; Wade, King, Wenden, Crawford, & Caldwell, 1998). The majority of patients are only seen once by a medical doctor immediately after mTBI and recover well over a period of several days to weeks. The treatment of the other ones coming back because of persistent symptoms highly depends on the experience with mTBI and available time of their general practitioner or the doctor on duty in the emergency department.

1.1.4.1. Neuropsychological consultation

Neuropsychological assessment of mTBI patients in the acute setting has been suggested to identify patients at high risk for prolonged cognitive deficits (Cushman et al., 2001) and to act as a treatment together with an information booklet to improve sleep and anxiety (Ponsford et al., 2002). Despite this, it is often not applicable in acute clinical practice to see all mTBI patients. If a patient suffers of persistent emotional symptoms or cognitive deficits, which keep him from returning to his pre-injury occupation, a consultation with a neuropsychologist might be recommended individually (Chang, Lombard, & Greher, 2011). Some objectives of a neuropsychological consultation can be: to objectify cognitive deficits, to gain further knowledge about emotional symptoms, to act as a cognitive performance test and to offer therapeutic intervention. The later can include education and reassurance with regard to the

natural course of recovery from mTBI, the role of complicating psychological factors, education about symptom reduction techniques like stress reduction exercises and support in the gradual resumption of premorbid activities. Several studies showed that specialised follow-up visits or calls additional to written information can lead to superior outcome in regard to PCS symptoms, stress respectively disruption of social activities (Mittenberg, 1996; Ponsford et al., 2002; Wade et al., 1998).

1.1.4.2. Imaging

Computer tomography (CT)

In emergency care, a cranial CT scan is still the gold standard for the detection of fractures, haemorrhages and mass effects in the acute phase after injury. A CT is fast, relatively inexpensive and widely available in emergency departments. A meta-analysis demonstrated that patients initially diagnosed with mTBI have pathological CT findings in approximately 8% of the cases dominated by haemorrhages (af Geijerstam & Britton, 2003). However, the CT is only a tool to exclude gross pathology and not a tool for prognostication of short- or long-term non-neurosurgical sequelae such as PCS (Wright, 2008).

Magnetic Resonance Imaging (MRI)

The MRI is more sensitive than the CT in detecting traumatic lesions during the acute phase of the injury (Paterakis, Karantanas, Komnos, & Volikas, 2000). Nevertheless, the correlation between focal structural lesions detected by conventional MRI and long-term patient outcome is controversial. Reason for this is that standard T1- or T2-weighted MRI may not be sensitive to the neuropathology of milder injuries (Hughes et al., 2004).

Susceptibility weighted imaging (SWI)

SWI is an imaging sequence that is acquired on a standard MRI scanner. It measures susceptibility differences between tissues and employs the phase image to detect these differences (Haacke, Xu, Cheng, & Reichenbach, 2004). It is sensitive to venous blood, haemorrhage and iron storage, which makes detection of traumatic cerebral microbleeds (MB) after mTBI possible and could thereby provide etiologic evidence for some post-traumatic neurological deficits (Park et al., 2009). This assessment can be obtained early after injury and may provide prognostic information regarding long-term outcome (Tong et al., 2004).

Diffusion Tensor Imaging (DTI)

Another promising MRI-technique, that is acquired on a standard MRI scanner and allows assessing of axonal integrity *in vivo*, is DTI. It measures the diffusion properties of water molecules in tissue and thereby provides quantitative markers of white matter lesions (Mori & Zhang, 2006). In healthy tracts the directionality of diffusion (=anisotropy) is higher than in less-organized grey matter, what allows for the generation of white matter fibre maps and calculation of fractional anisotropy (FA) - the directional preference of diffusion (Le Bihan et al., 2001). Other measures that are frequently calculated based on DTI are the mean diffusivity (MD) – calculated by the mean of the three eigenvalues, the axial diffusivity (AD) - the diffusivity along the principal axis and the radial diffusivity (RD) - the averaged diffusivities in the two minor axes (Soares, Marques, Alves, & Sousa, 2013). Subsequently, FA has been shown to be sensitive to microstructural changes in white matter integrity in mTBI patients (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008). A growing number of studies compare cognitive status with DTI findings in mTBI patients (Kraus et al., 2007; Kumar et al., 2009; Mayer et al., 2010; Messe et al., 2011; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008; Wang et al., 2011; Wu et al., 2010). Some of the published studies with mTBI patients concluded that microstructural white matter lesions detected by DTI correlate with persistent cognitive deficits in mTBI (Messe et al., 2011; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008; Wang et al., 2011). The exact mechanisms that cause changes in DTI measures post-injury are, however, not fully understood. Past studies emphasized the need for longitudinal studies to allow better assessment of the time course of DTI changes in mTBI, correlations between DTI changes and neuropsychological outcome and PCS, and possible use as prognostication tool.

1.1.5. Current clinical management

Despite the frequency of mTBI, no clear and consistent standard management practices or interventions exist within the emergency departments worldwide (Adirim, 2007). As a result, there have been efforts in several countries to write guidelines for the treatment of mTBI based on research and clinical experience from the last decades (e.g. (Marshall et al., 2015; New South Wales Motor Accident Authority, 2008). The primary objectives of the emergency department clinician are the proper detection and diagnoses of mTBI (including the identification of patients requiring neurosurgical intervention) and to give early guidance. To reach the first objective the medical history including mental health and current symptoms should be assessed and a physical examination should be performed. For many of the mTBI patients the assessment

at the emergency department is their only contact with the health care system (Bazarian, Hartman, & Delahunta, 2000). To reach the objective of early guidance, verbal and written instructions should be given to the patients, respectively to their caregivers. Those should contain information on common symptoms associated with mTBI, reassurance about the anticipated benign recovery process, instructions on how to gradually return to everyday activities and coping strategies such as techniques to manage stress, as well as symptoms and signs, which call for a follow-up with a medical doctor (Levin & Diaz-Arrastia, 2015; Marshall et al., 2015). There is general agreement that in case of headaches immediately post-injury, a prescription for an analgesic should be handed out. Further guidance from the emergency department clinician is probably expected from most patients in regard of the duration of sick leave including a doctor's certificate. The next chapter places special emphasis on the assignment of sick leave and the time until return to preinjury activities such as work or school. At the Cantonal Hospital of St.Gallen the standard care of mTBI patients besides the study consisted of the recording of a medical history including current symptoms by means of a standardized form for mTBI patients and an examination by a neurosurgeon on duty, as well as possibly a CT-scan according to the Canadian CT Head Rules (Stiell et al., 2001). Patients not requiring further neurosurgical intervention and/or monitoring received an information sheet on mTBI, as described above, and a prescription for analgesic. The development of the information sheet was part of this scientific project. Staff members from the emergency and the neurosurgery department together with the PhD student as representative of the neuropsychological department developed the information sheet based on current knowledge. Patients not participating in the study received a recommendation on when to return to work by means of a doctor's certificate issued on the judgement of the neurosurgeon on duty. Patients returning to the emergency department or their general practitioner with persistent cognitive deficits or PCS beyond the acute phase and troubles to return to work or school were occasionally sent for a neuropsychological assessment and ambulant therapy.

1.1.6. Duration of sick leave and return to work or school

A survey among European hospitals (67 questionnaires were received from 21 European countries) showed major differences in management with regard to the ordering of bed rest, home observation, sick leave and follow-up examination (Kruijk, Twijnstra, Meerhoff, & Leffers, 2001). Sixty-four percent gave their mTBI patients sick leave, six percent did not and in 30 percent it was unknown. The duration of sick leave varied between one and 30 days. Clinical practice guidelines for mTBI patients recommend that patients who report symptoms

immediately after the injury should have an initial period with a restful pattern of activity throughout the day with minimal physical and mental exertion (Management of Concussion/mTBI Working Group, 2009), while bed rest exceeding three days is not recommended (Silverberg & Iverson, 2013). None of the guidelines name a specific number of days for the resting period, but there seems to be a general agreement that the first 72 hours post-injury are the most acute when it comes to symptom severity, also keeping pathophysiological processes in mind, and therefore three days of rest seems to be the minimum. However, no randomised trial has been published on the value and duration of sick leave immediately after mTBI so fare, despite each doctor having to decide if he hands out a doctor's certificate for sick leave and if so for how long.

After the initial period of rest, patients should be encouraged to gradually return to their normal activities including work, school, physical and leisure activities as soon as tolerated, while still avoiding activities with increased risk for sustaining another brain injury. Even when patients return to their preinjury activities such as work and school they may be experiencing symptoms (van der Naalt, van Zomeren, Sluiter, & Minderhoud, 1999) and the loading capacity may be reduced compared to their preinjury level for several weeks. In this PhD-project the expression "return to work" was also used for students and housewives.

Since specific recommendations on the duration of sick leave for mTBI patients are missing, information about the time until return to work were searched. Most medical personnel working with mTBI patients would probably agree that the majority of individuals, which were employed or studying at the time of injury, return to work within a year of injury. Despite this, the estimates of individuals who are able to return to their occupation within a year of the injury range from 73 to 88% between studies (Dikmen et al., 1994; Nolin & Heroux, 2006; van der Naalt et al., 1999). Looking at the time until return to work in more detail a study reported that at their follow-up two weeks post-injury 44% of their sample had returned to work, while in the follow-up six weeks post-injury it was a total of 62% (Haboubi, Long, Koshy, & Ward, 2001). Another study reported that 87% of their sample of 816 workers benefited of a single episode of wage replacement for a median duration of 11 days before returning to work (Kristman et al., 2010). The remaining 13% had at least two periods with wage replacement with a median time ranging from just over two months to more than seven months. A Canadian study found a median of 3.5 days respectively a mean of 72.2 days to return to work in their mTBI patients not seeking financial compensation compared to a median of 42.5 days, respectively a mean of 113.7 days in their group seeking or receiving compensation benefits,

disability or sick leave payments (Reynolds, Paniak, Toller-Lobe, & Nagy, 2003). A more recent study found a median of six days off work for mTBI patients without intracranial abnormalities in the CT or MRI compared to a median of 36 days for mTBI patients with intracranial abnormalities in the CT or MRI (Iverson et al., 2012).

From the summarized numbers it is difficult to gain a clear overview of expected time until return to work since some studies reported return to work status (returned versus not returned) at a certain time of follow-up, others median respectively mean of days until return to work. Other studies focused on return to work numbers in regard of a potential influence factor. This points out the question, what factors apart from financial compensation-seeking status and intracranial abnormalities could influence return to work after mTBI? A 90% chance of full return to work six months post-injury was reported in patients with over eleven years of formal education, without nausea or vomiting on hospital admission, with no extracranial injuries and only low levels of pain early after injury (Stulemeijer, van der Werf, Borm, & Vos, 2008). Other researchers found that mTBI patients had a higher return to work rate if the job had greater independence and decision-making latitude (Friedland & Dawson, 2001). Drake, Gray, Yoder, Pramuka, and Llewellyn (2000) found three cognitive variables (verbal memory, verbal fluency and a speed test) to be predictive of work status three to 15 months following mTBI, correctly classifying work status 68.8% of the time. The greatest number of symptoms were found in individuals who had not returned to work one year or more post-injury in a study of Nolin and Heroux (2006). These studies show that there is a long list of potential factors influencing the duration of time until return to work.

2. THE CURRENT STUDY

In the following section, the rationale, aims and research questions of this PhD project, as well as the study population of the two original research articles (paper 2 and 3), are described. Subsequently, the three publications that form the empirical basis of this PhD thesis are presented. Each publication begins with an introduction to the current knowledge of the respective topic as well as the rationale. This is followed by methodological information on the literature review (paper 1), respectively on the original research (paper 2 and 3). The results are first individually presented and discussed in the corresponding publication section, and then more globally integrated in a general discussion and conclusion (chapter 3).

2.1. Rationale, aims and research questions

Since mTBI is one of the most common neurological disorders diagnosed in emergency departments and PCS accompanies a significant number of patients beyond three months post-injury, this leads to immense socio-economic burdens for the patients, their relatives as well as for the whole community. The idea for this PhD project arose due to missing clear and consistent standard clinical management practice for mTBI patients. In a first step, the identification of patients at risk for pPCS after mTBI is an important precondition to be able to support them with guidance and early treatment, since this has proven to lead to fewer reported pPCS (Bell et al., 2008; Ponsford et al., 2002; Wade et al., 1998). During the conception phase of this study the discussion about diagnostic measures acquired with MRI to identify patients at risk for pPCS was in its rise in the scientific community, while their clinical suitability was questioned. In a second step, specific guidelines based on empirical data on when to return to pre-injury activities are of paramount importance for all patients, since it probably influences their recovery and their work, school, sport and social environment. The scarce data on return to work after mTBI and the complete lack of prospective randomized studies on the most beneficial time until return to work was therefore the second rationale why this scientific project was initiated in the first place. The aims of the current study were to:

1. Review and evaluate diagnostic techniques acquired on a standard MRI scanner in the prediction of pPCS and unfavourable cognitive outcome and to learn more about the pathophysiology of mTBI over the duration of one year post-injury (see paper 1 for a review and paper 2 for results of the empirical project).
2. Evaluate the influence of two recommended specific times, respectively the effective time until return to work or school on the development of PCS and cognitive outcome over a period of one year with follow-ups in the acute (within seven days), the semi-acute (after three months) and the late phase post-injury (after twelve months) (see paper 3 for results).

We divided both aims each in two research questions.

Research question 1: Which MRI-techniques are able to predict* pPCS *and unfavourable cognitive outcome in patients with mTBI?

We approached this first research question in two ways. First, we performed a literature review to find out what other researchers have found to answer this question. Second, we examined the recruited mTBI patients with the MRI-techniques SWI and DTI, within one week post-

injury to evaluate if those techniques are able to predict pPCS and unfavourable cognitive outcome as measured in an extensive neuropsychological test battery after three and twelve months. We had chosen to focus on the two MRI-techniques SWI and DTI based on the knowledge gain of the literature review and keeping clinical practicability in mind.

Research question 2: What can we learn about the pathophysiology of mTBI over the period of one year by means of MRI and specifically SWI and DTI?

The SWI- and DTI-data of the mTBI patients from the acute and late phase post-injury were each compared to data of a group of healthy controls (CTRL) to reveal pathological processes. Additionally, the SWI- and DTI-data from the acute and the late phase post-injury from the mTBI patients were compared to learn more about the course of the pathophysiology over the time of one year within the group of mTBI patients.

Research question 3: Is a short or intermediate time to return to work after mTBI more favourable with regard to pPCS and cognitive outcome?

We assume that an intermediate period of mental and physical relief by helps of sick leave from work or school enables the cascade of neurochemical changes after mTBI to normalise. This probably allows a faster recovery and successful return to work, less individual and socio-economic burden, lower incidence of PCS and overall higher patient satisfaction. For this third research question we randomly allocated the recruited mTBI patients with either a doctor's certificate recommending three or seven days until return to work and compared the cognitive outcomes and the pPCS between those two groups after three and twelve months.

The recommended times to return to work (either three or seven days) were selected on the basis of current knowledge about the neurophysiological and neuropsychological recovery from mTBI and the influence of rest for the recovery. Three to five days post injury most of the neurometabolic cascade is back to the normal level and after ten days even the cerebral blood flow is said to be back to normal (Giza & Hovda, 2001, 2014). Maximal symptoms are typically experienced within the first 72 hours and functioning improves rapidly within the first week ((Iverson, 2005). Prospective studies in sports concussion showed that athletes' cognitive performance returned back to baseline during a three to seven day interval (Bleiberg et al., 2004), respectively within 7 days (McCrea et al., 2003) after having shown initial cognitive difficulties. A scientific review pointed out that bed-rest exceeding three days is not

recommended and the resumption of preinjury activities (except the ones with high preinjury risks) should begin as soon as tolerated (Silverberg & Iverson, 2013).

Research question 4: How does the effective time until return to work influence pPCS and cognitive outcome?

Since we expected that some patients would not (be able) to obey to the recommendation on when to return to work, we enquired the effective time until return to work from the patients at follow-ups. We analysed the influence of effective time until return to work on pPCS and cognitive outcome three and twelve months post-injury.

2.2. Study population

The results of the two original papers (paper 2 and 3) are based on the same study population. MTBI patients for the current study were all recruited at the emergency department of the Cantonal Hospital St.Gallen between August 2012 and December 2013. Our goal was to recruit a sample of 66 mTBI patients during this time based on the following power calculation:

> A power calculation by t-test with two-sided significance level 0.05 will have 80% power to detect a difference in PCS score (measured with ImPACT) between the 'three days return to work' group and the 'seven days return to work' group of nine points, where the common standard deviation is ten, at three months post-injury when the sample size in each group is 33 patients (66 total).

More details on recruitment and data collection are provided in papers 2 and 3.

2.3. Paper 1: Diagnostic approaches to predict persistent posttraumatic symptoms after mild traumatic brain injury – a literature review[1]

2.3.1. Introduction

Mild traumatic brain injury is one of the most frequently diagnosed neurological disorders in emergency departments worldwide. Historically, the diagnosis of mTBI has been very challenging, due to the continuing debate over the clinical definition (Bigler & Bazarian, 2010) and because the diagnosis is dependent on the patient's subjective self-report (Maruta et al., 2010). This self-report of deficits may be underreported by the patient's reduced awareness of limitations. Moreover, the desire to return to play or duty, cultural issues that discourage symptom report, symptoms that are not immediately apparent but develop or worsen over days to weeks, and finally potential costs of urgent medical care in some countries for symptoms which the patient or family do initially not feel life-threatening or worrisome, among others, are also factors that may lead to underreporting (Meier et al., 2014).

Persistent posttraumatic symptoms, including neuropsychological impairments, persisting physiological complaints and psychiatric symptoms, are often summarized as PCS. The usefulness of PCS in the assessment of mTBI remains unclear due to the non-specificity of these symptoms and the fact that a given percentage of the normal population report these symptoms even in the absence of a traumatic event (Chen, Johnston, Collie, McCrory, & Ptito, 2007). Recently, Waljas et al. (2014) reported that 31% of their healthy control sample met PCS criteria. According to their results, significant predictors of PCS at one month were pre-injury mental health problems and the presence of extra-cranial bodily injuries. Also, being symptomatic at one month was a significant predictor of still being symptomatic at one year, and depression was significantly related to PCS at both one month and one year. Additionally, the incidence of PCS after mTBI varies widely, partially because of the difference in diagnostic criteria for PCS (Boake et al., 2005). Recent findings suggest that in mTBI patients, 64% using ICD-10 criteria and 11% using DSM-IV criteria have PCS three months post-injury (Boake et al., 2005). The long-term prevalence of PCS after mild brain trauma is estimated between 15 and 30% (Hou et al., 2012). These persisting complaints may disrupt the patients' social relationships and their ability to resume leisure and work-related activities (van der Naalt,

[1] Studerus-Germann, A. M., Thiran, J. P., Daducci, A., & Gautschi, O. P. (2016). Diagnostic approaches to predict persistent post-traumatic symptoms after mild traumatic brain injury - a literature review. *Int J Neurosci*, *126*(4), 289–298. doi:10.3109/00207454.2015.1033620

2001). mTBI patients with pPCS may have greater neuropsychological impairments than those without pPCS (Sterr, Herron, Hayward, & Montaldi, 2006). Studies of Sheedy et al. and Faux et al. found that immediate verbal recall and quantitative recording of headache was able to predict PCS with a sensitivity of 80%, respectively 71.4%, and a specificity of 76%, respectively 64.2% in an Australian and Canadian population (Faux & Sheedy, 2008; Sheedy, Geffen, Donnelly, & Faux, 2006). The assumption for the development and persistence of PCS is that metabolic and structural changes in the brain of mTBI patients have not returned to homeostasis (Willer & Leddy, 2006). There is a trend that earlier intervention (e.g. psychosocial intervention) is more likely to improve outcome (Ponsford et al., 2002; Wade et al., 1998). Therefore, the identification of patients who might continue to have pPCS and who should be offered early treatment is of paramount importance.

Though CT is the gold standard to detect intracranial abnormalities in the emergency setting, it is not a tool for prognostication of short- or long-term non-neurosurgical sequelae such as PCS (Wright, 2008). Additionally, MRI is more sensitive than CT in detecting traumatic lesions during the acute phase of injury (Paterakis et al., 2000). Nevertheless, the correlation between focal structural lesions detected by conventional MRI and long-term patient outcome is controversial, since T1- or T2-weighted MRI sequences may not be sensitive to microstructural neuropathology of milder injuries (Hughes et al., 2004). Another study showed, however, that an approach to identify and count individual patho-anatomic features on MRI such as brain contusions and foci of haemorrhagic axonal injury could be predictive of a poorer three-months outcome in mTBI (Yuh et al., 2013). One or more brain contusions on MRI, and four foci of haemorrhagic axonal injury on MRI, were each independently associated with poorer three-months outcome as measured with the Extended Glasgow Outcome Scale (GOS-E) (Yuh et al., 2013). Recently, SWI has been found to be useful to detect MB after mTBI as a marker of DAI. It has been shown to provide etiological evidence for some post-traumatic neurological deficits that were unexplainable in conventional MRI (Park et al., 2009). Furthermore, the quantity and volume of SWI-detected bleeds suggestive of haemorrhagic DAI seem to be an important factor determining long-term cognitive and neuropsychiatric disability following TBI (Adams, Graham, Murray, & Scott, 1982; Medana & Esiri, 2003). This assessment can be obtained immediately after injury and may provide prognostic information regarding long-term outcome (Tong et al., 2004). Another promising, more recent MRI-technique, is DTI, which can be used to detect alternations in the white matter ultrastructure allowing the generation of three-dimensional reconstructions of white matter tracts and brain structural connectivity (Kumar,

Rao, Chandramouli, & Pillai, 2009). DTI has been shown to be more sensitive for DAI than conventional MRI (Arfanakis et al., 2002). A third evolving MRI-technique is Magnetic Resonance Spectroscopy (MRS), which provides information about metabolism in small regions of the brain. Preliminary data show that Creatine-Phosphocreatine (Cr) levels measured with MRS in the subacute stage after mTBI are predictive of cognitive outcome and emotional distress (Gasparovic et al., 2009). Another imaging method, the functional Magnetic Resonance Imaging (fMRI) analyses regional changes in haemodynamic activity, most frequently using the blood oxygenation level-dependent (BOLD) signal. The role of fMRI in the management of mTBI is still limited (Seeley, Crawford, Zhou, Miller, & Greicius, 2009).

This literature review addresses the questions which of the named diagnostic approaches (SWI, DTI, MRS, and fMRI) may predict pPCS in adults with mTBI.

2.3.2. Methods

A thorough literature search for experimental studies focused on mTBI and neuroimaging published from January 2000 up to September 2014 was performed on PubMed on the 30th of September 2014. The search included the following keywords: (1) "mild traumatic brain injury" and (2) "susceptibility-weighted imaging" or "diffusion tensor imaging" or "magnetic resonance spectroscopy" or "functional magnetic resonance imaging" and (3) / "post-concussion symptoms" / or "cognitive outcome". Further studies meeting the inclusion criteria were identified from the reference lists of included articles.

Inclusion criteria: Articles were included if they evaluated one of the following diagnostic approaches (1) SWI, (2) DTI, (3) MRS, and/or (4) fMRI as predictive factors of pPCS or cognitive outcome in adult populations with mTBI. The search was limited to English language studies. *Exclusion criteria:* Studies focussing merely on paediatric patients were excluded because of the on-going brain development of children and adolescents and the variability in the pattern of PCS depending on age. Also excluded from the present review were studies with a focus only on blast-related mTBI as the injury mechanism is not fully understood yet. Studies that mixed mTBI with moderate or severe TBI or where the severity of injury was not clearly specified in the full article were excluded. Studies focusing on other MRI-sequences as the ones specified in the inclusion criteria were excluded. Finally, case reports, interventional studies and reviews were excluded.

2.3.3. Results

Overall, the literature search identified 127 articles trough database searching plus three articles trough the reference sections of those articles addressing diagnostic approaches to predict pPCS after mTBI (Figure 1). After removal of duplicates, 104 titles and abstracts were screened, of which 61 were excluded because they met one or more of the above exclusion criteria. Of the retrieved and assessed 43 relevant full papers, 18 were removed because they met one or more of the above exclusion criteria. A total of 25 studies were finally included in the qualitative synthesis, 1 focusing on SWI and DTI, 1 on MRS and fMRI, 2 merely on SWI, 16 merely on DTI, 2 merely on MRS and 3 merely on fMRI.

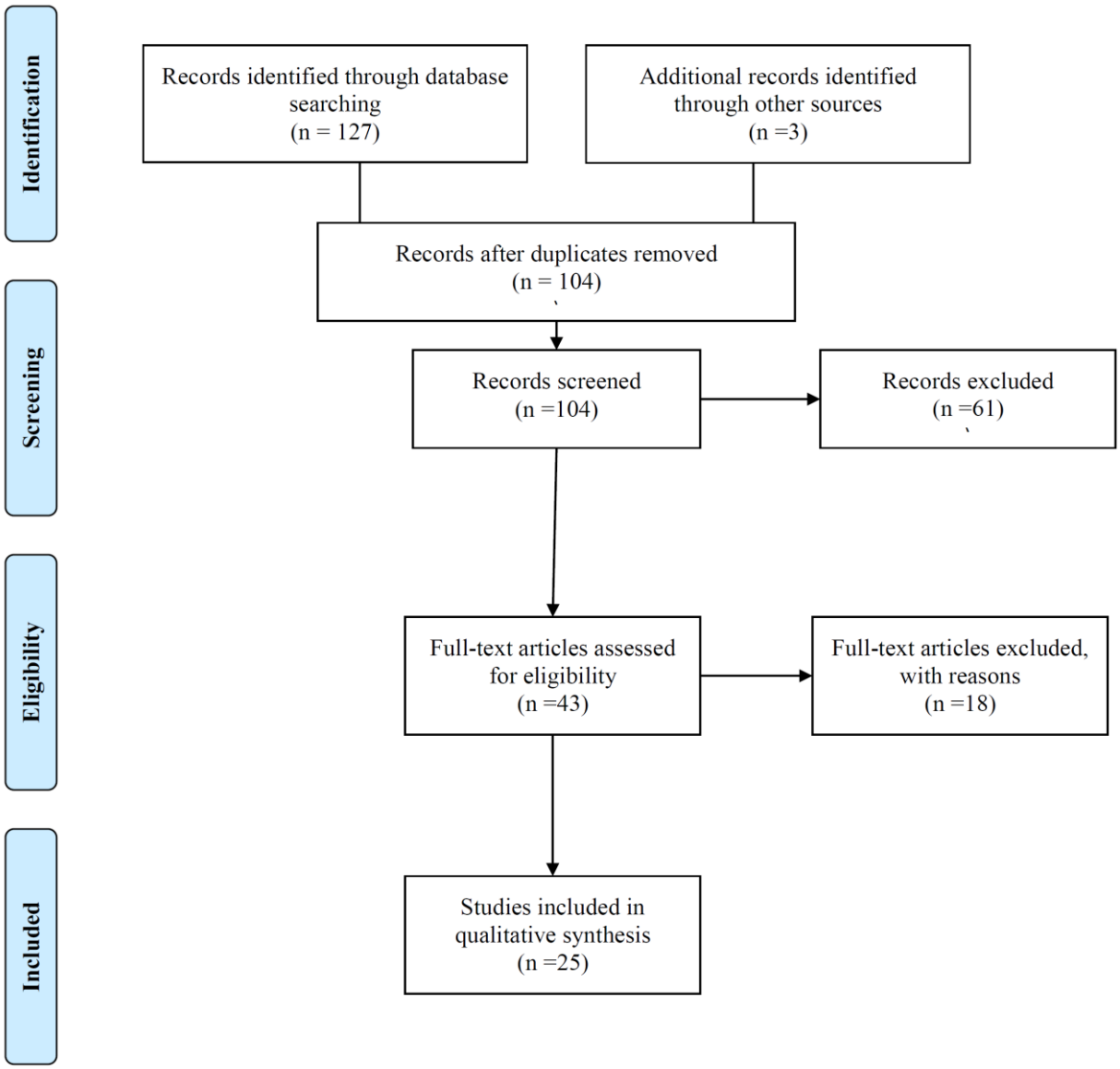


Figure 1. Flow diagram of literature search.

Susceptibility-weighted imaging (SWI)

Traumatic cerebral MB have shown characteristic regional distributions and associations with initial neurological status and prognosis after mTBI (Park et al., 2009). Microbleeds in mTBI were found to be located more frequently in white matter than in deep nuclei compared to a control group (Park et al., 2009). The presence and quantity of MB in mTBI patients were closely related with lower scores on the GCS on the day of trauma and on the Glasgow Outcome Scale (GOS) one year post-injury (Park et al., 2009). Toth et al. did not find micro haemorrhages in their mTBI patients with SWI and did not perform any questionnaires or assessments to measure pPCS (Toth et al., 2013). Contra wise, Kou et al. found in three of nine patients with mTBI intracranial haemorrhages on SWI, all of them had very high glial fibrillary acidic protein (GFAP) levels (Kou et al., 2013).

Diffusion Tensor Imaging (DTI)

DTI has demonstrated that mTBI is associated with wide-spread structural changes in cortical white matter tracts and the integrity of those have been shown to correlate with behavioural and cognitive measures (Arfanakis et al., 2002; Huisman et al., 2004; Kraus et al., 2007; Lipton et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008; Ptak et al., 2003; Rugg-Gunn, 2001; Rutgers et al., 2008). According to recent literature, changes in diffusivity indexes may indicate different types of white matter abnormality and different stages post-injury after mTBI (Bigler & Bazarian, 2010; Niogi & Mukherjee, 2010). Higher fractional anisotropy (FA) in mTBI compared to controls may reflect an inflammatory response such as axonal swelling or cytotoxic oedema (Bazarian et al., 2007; Chu et al., 2010; Mayer et al., 2010). Decreased FA in mTBI compared to controls may indicate axonal degeneration and discontinuities with excess water between tracts or in perivascular spaces (Bigler & Bazarian, 2010; Lipton et al., 2008). These findings have been confirmed by Kou et al. who reported that FA values could both increase or decrease in the acute setting (Kou et al., 2013). DTI findings of the first week post-injury provide evidence that in the acute state FA normally increases and/or radial diffusivity (RD) decreases and/or mean diffusivity (MD) decreases (Chen et al., 2012; Chu et al., 2010; Mayer et al., 2010; Toth et al., 2013; Wilde et al., 2009; Wu et al., 2010). More than two weeks post injury, either a decrease in FA or an increase in MD or a combination of both is seen more common (Cubon, Putukian, Boyer, & Dettwiler, 2011; Inglese et al., 2005; Kinnunen et al., 2011; Smits et al., 2011). Recently, Zhu et al. suggested that decreased FA probably indicates the original damage to the axon and the increased one indicates recovery, and that an increase in FA may indicate more severe TBI correlated with poor clinical outcomes

(Zhu et al., 2014). Unfortunately the time difference between studies more than two weeks post-injury is very heterogeneous, ranging from a mean of 17 days up to 35 months (Benson et al., 2007; Messe et al., 2011).

By means of more recent DTI analysis techniques, such as automated region of interest (ROI) analysis, tract-based voxel-wise analysis and quantitative tractography, frontal and temporal association white matter pathways have been found to be the most frequently damaged (Niogi & Mukherjee, 2010). Messé et al. found damage to long association fasciculi connecting frontal, parietal and temporal cortices to represent the main pathological substrate of PCS (Messe et al., 2011). Patients with persistent PCS had significantly higher mean RD values in long association white matter fibre tracts. They also found changes in MD following mTBI and interpreted that MD is the most sensitive diffusion variable to measure the early occurrence of DAI following mTBI and to predict the clinical outcome. Chu et al. found a decrease in MD and RD and an increase in FA scores in mTBI patients with increased pPCS scores at a range of one to six days post-injury (Chu et al., 2010). They suggest that damage to white matter and its interconnectivity by means of mTBI may be associated with pPCS. On the other hand, however, Bouix et al. reported an abnormally low FA in white matter and an increased grey matter FA in patients with pPCS following mTBI (Bouix et al., 2013). The authors explain this novel in-vivo finding in grey matter FA with an animal model of brain trauma that associates increased FA in grey matter with pathologies such as gliosis. Lange et al. did not find any significant differences in white matter integrity in the corpus callosum between mTBI patients who met the criteria for PCS and the ones who did not meet them two months post-injury (Lange et al., 2015).

A growing number of studies compare DTI findings with cognitive status (Kinnunen et al., 2011; Kraus et al., 2007; Mayer et al., 2010; Messe et al., 2011; Miles et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008; Wu et al., 2010). The largest published DTI study with mTBI patients (n= 43) and cognitive assessment concluded that microstructural white matter lesions detected by DTI correlate with persistent cognitive deficits in mTBI (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008). Kinunnen et al. found that the location of white matter damage measured with DTI potentially predicts cognitive function (Kinnunen et al., 2011). Associative learning and memory was related to the structure of the fornices in the way that patients with increased FA performed better on memory testing. Executive function was related

to frontal lobe connections, patients with high MD in the left superior frontal white matter showed worse performance in executive function. Whilst Kinunnen et al. did not find a relationship between their measures of executive function and FA, Niogi et al. reported a correlation between attention control as a measure of executive function and FA in the left hemisphere anterior corona radiata in mTBI patients (Kinnunen et al., 2011; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008). Additional to that memory performance of mTBI patients was correlated with FA in the uncinate fasciculus in the study of Niogi et al. (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008). Interestingly, Fakhran et al. found sex differences in white matter abnormalities after mTBI (Fakhran, Yaeger, Collins, & Alhilali, 2014). The authors found a relative sparing of the uncinate fasciculus in female compared with male patients after mTBI. The authors concluded that sex and uncinate fasciculus FA values are independent risk factors for pPCS after three months and stronger predictors of time to symptom resolution than initial symptom severity. Wu et al. found a correlation between FA and memory performance, specifically they found that increased FA of the left cingulum bundle correlated with poorer memory performance in mTBI patients tested approximately three days post-injury (Wu et al., 2010). Miles et al. reported a trend toward a significant correlation between baseline MD measured at an average of four days post-injury and response speed at six months follow-up as well as a positive correlation between baseline FA and a measure of executive function (Miles et al., 2008). Niogi et al. found that the number of damaged white matter structures measured by DTI was significantly correlated with mean reaction time on a cognitive task (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee et al., 2008). Kraus et al. found that in a sample tested at a mean of 92.6 months post-injury a greater number of regions with reduced FA predicted greater cognitive impairments in executive function, attention and memory (Kraus et al., 2007). They found reduced FA in the cortico-spinal tract, sagittal stratum and superior longitudinal fasciculus. They concluded that white matter changes might be primarily due to axonal damage rather than myelin damage. In a study of Mayer et al., a significantly greater FA as a result of reduced RD in the corpus callosum and several left hemisphere tracts within 21 days post-injury, was not correlated with poor neuropsychological test performance (Mayer et al., 2010).

The exact mechanisms that cause changes in DTI measures and lead to correlations with cognitive impairment are still not fully understood. Unfortunately, different neuropsychological tests were used to characterize the cognitive domains that seem most prone to white matter injury – executive function, memory and attention/information processing speed – which makes a comparison between studies difficult.

Magnetic Resonance Spectroscopy (MRS)

MRS-detectable N-acetyl aspartate (NAA) levels reflect both axonal integrity and independent cellular processes, such as mitochondrial disturbances (Kirov et al., 2013). With MRS, lower levels of white matter NAA have typically been found in mTBI patients compared to healthy controls or to the uninjured brain side in the acute phase after injury (Chen et al., 2012; Son et al., 2000). These results have been interpreted to reflect neuronal loss, metabolic dysfunction or myelin repair (Gasparovic et al., 2009). Recovery from NAA/creatine (Cr) was found 30 days after injury by Vagnozzi et al. (Vagnozzi et al., 2008). The initially reduced NAA returned to a nearly normal level by two months post-injury (Son et al., 2000). Since NAA was sampled from areas, which showed white/grey pericontusional lesions on CT, the recovery rate might be faster in patients with normal CT findings. Chen et al. additionally found reduced NAA/Cr in 13 cases and increase of lactic acid (Lac) in seven cases of 19 examined mTBI patients (Chen et al., 2012). Gasparovic et al. found higher levels of white matter Cr-phosphocreatine in mTBI patients in the early sub-acute phase (three to 19 days post-injury) compared to healthy controls and the Cr levels were predictive of executive function and emotional distress (Gasparovic et al., 2009). In mTBI patients the combined glutamate and glutamine signal (Glx) were significantly lower and the Cr levels significantly higher compared to healthy controls (Gasparovic et al., 2009). Similarly, Henry et al. showed a significant decrease in glutamate in the primary motor cortex (M1), as well a significant decrease in NAA in the prefrontal and primary motor cortices in a group of twelve concussed athletes (Henry, Tremblay, Boulanger, Ellemberg, & Lassonde, 2010). At the late subacute (> one month post-injury) and chronic (> six months post-injury) stages of mTBI, George et al. found decreases in choline-to-creatine ratio (Cho/Cr) measured in the thalamus and centrum semiovale (George et al., 2014). Their results from the early sub-acute phase (within ten days post-injury) showed positive associations between Cr measurements in the centrum semiovale with performance on cognitive assessment in immediate and delayed code substitution as a measure of visual search and learning respectively recognition and memory by means of Automated Neuropsychological Assessment Metrics (ANAM).

The findings of these three studies including MRS and cognitive assessment, respectively emotional measure, show that metabolic measures can potentially serve as diagnostic and prognostic markers of mTBI. Also the study from Henry et al. including ten concussed and ten non-concussed athletes confirmed cortical neurometabolic changes in the acute post-concussion phase as well as recovery and continued metabolic abnormalities in the chronic phase (Henry et al., 2011).

Functional magnetic resonance imaging (fMRI)

Chen et al. designed a study to define the relationship between self-reported PCS, neuropsychological performance and fMRI activation in a group of concussed athletes with persisting PCS (Chen et al., 2007). This study including 28 male athletes with and without concussion grouped according to their PCS score showed reduced task related activation patterns in the dorsolateral prefrontal cortex for both low and moderate PCS groups during a working memory task. The authors reported that the severity of PCS predicted the fMRI BOLD signal changes in cerebral prefrontal regions. By comparing the brain activation maps, a clear difference could be seen between the control group and concussed athletes with an additional activation peak in left temporal lobe during verbal working memory task in the concussed individuals. Additionally, they found an inverse relationship between PCS scores and cognitive performance on several subtests of a computerised cognitive test battery. Their results support the use of the PCS scale as diagnostic measure after mTBI and the use of brain activation maps to differentiate between athletes with and without concussion. Similarly, Slobounov et al. performed an fMRI study evaluating spatial memory including 15 athletes suffering from mTBI, however, without persisting PCS (Slobounov et al., 2010). The quantitative analysis of BOLD signal revealed that concussed individuals had a significantly larger cluster size during encoding at parietal cortex, right dorsolateral prefrontal and right hippocampus. Messé et al., on the other hand, investigated 17 mTBI patients with persistent PCS at six months post-injury compared with 38 mTBI patients with no PCS and 34 healthy controls using a resting-state fMRI (Messe et al., 2013). The authors could demonstrate an increased connectivity in temporal regions and decreased connectivity in frontal regions in mTBI patients with PCS.

In summary, the results of the above fMRI studies show that concussed individuals show additional activation peaks (Chen et al., 2007) and larger cluster size (Henry et al., 2011) compared to healthy controls during cognitive task conditions. The results of the study of Messé et al. have shown fMRI as a useful tool to differentiate mTBI patients with PCS from controls and mTBI patients without PCS in a resting-state condition by means of changed connectivity (Messe et al., 2013).

2.3.4. Discussion

The lack of consistency of criteria to define mTBI and the diversity of populations leads to a wide heterogeneity among the included subjects (Pertab, James, & Bigler, 2009). The methods and questionnaires used to measure pPCS varied between studies and with it the criteria chosen

for PCS, which made a comparison of PCS difficult. This was an initial reason for us to choose pPCS instead of PCS as outcome variable for the purpose of this review. An open question for all mentioned diagnostic approaches is how many hours, days or weeks post-injury should patients with mTBI be examined that pPCS can be predicted best. Cortical changes across the human lifespan have rarely been taken into consideration when interpreting imaging results of mTBI studies, though it is known that the brain in healthy adults changes during lifespan. All diagnostic measures based on MRI have weaknesses in availability, capacity and costs. Diagnostic measures based on MRI vary greatly on MRI characteristics, such as spatial resolution, magnetic field strength, sequence parameters and image post-processing. This has to be taken into account when comparing and interpreting study results.

Susceptibility-weighted imaging (SWI)

The detection of traumatic cerebral MB seems to be predictive of the prognosis after mTBI. The strength of SWI is that it can be analysed efficiently by a neuroradiologist in clinical setting. Future studies should investigate if adult patients with a higher number of MB measured with SWI are at risk for specific neuropsychological impairments, as could be shown in a study with paediatric patients when the number of MB exceeded seven or more regions (Tong et al., 2008). It should, moreover, be investigated if the size of MB is predictive of pPCS. However, MB can also be found in cerebrovascular disease, dementia and in normal ageing, therefore their occurrence in mTBI patients might not be due to the traumatic incidence but due to pre-existing diseases.

Diffusion Tensor Imaging (DTI)

Obviously, DTI is a very promising tool to quantify mTBI in the acute, subacute and chronic phase. The time difference between (m)TBI and DTI scanning is an important factor in the interpretation of DTI results (Bouix et al., 2013). In some studies mTBI patients with a very wide range of different times post-injury ranging from some months to several years are examined with DTI and compared with each other in one group (Lipton et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee et al., 2008; Rutgers et al., 2008). We believe that this leads to biased data as the DTI values change over time, as can be seen in studies which compared several time-points (Arfanakis et al., 2002; Mayer et al., 2010; Messe et al., 2011; Miles et al., 2008). More knowledge is needed on the best time window to scan mTBI patients with DTI to predict pPCS. A major limitation of past DTI-studies on mTBI is their small sample sizes (Lipton et al., 2008; Messe et al., 2011; Miles et al., 2008; Wilde et al., 2009; Wu et al.,

2010). This leads to limited statistical power of the statistical analysis of DTI and cognitive data. For example for voxel-based morphometric analysis, the statistical power is largely influenced by the sample size (Messe et al., 2011). In ROI analysis of DTI data the small sample sizes prevent from investigating regional differences in focus regions. In the study of Wu et al. the small sample size of twelve mTBI patients did not permit an investigation of regional differences within the cingulum bundles (Wu et al., 2010).

The methods of analysis of DTI data varies between studies and their comparability should be further studied. There is no agreement as to which analysis method is the best for mTBI patients in clinical and research setting. The regional approach to discriminate controls and mTBI is thought to be the better method than the whole-brain white matter approach and might be a better predictor of cognitive outcome according to Benson et al. (Benson et al., 2007). So far, ROI-analysis is used most often in mTBI-studies and it is said to be appropriate for individual analysis (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee et al., 2008). A limitation of it is that it only samples a pre-defined, restricted number of regions, ignoring the diffusivity of axonal damage and the placement of ROI is dependent on the analyst. Another approach is the voxel-based analysis, which is independent from the analyst, fast and suited for group analysis, whilst its suitability for individual analysis has yet to be evaluated and there are concerns about errors that may occur from the required spatial normalization and co-registration processes (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee et al., 2008). A voxel-wise approach reduces potential biases by standardizing the analysis and improves sensitivity by minimizing partial volume effects (Lipton et al., 2008). Kinnunen et al. were the first to evaluate the relationship between white matter damage measured with tract-based spatial statistics (TBSS), a new voxel-based technique, and cognitive impairment following TBI (Kinnunen et al., 2011). Toth et al. also used TBSS in their recent study and concluded that the semi-automated method is suitable for clinical practice (Toth et al., 2013). Equally using a TBSS approach, Zhu et al. observed a loss of structural integrity in multiple brain domains in acute symptomatic mTBI patients, who presented decreased FA values in widespread regions specially located in frontal lobe, limbic system and sublobar areas compared with a healthy control group (Zhu et al., 2014). So far analysis of DTI data is quite time consuming and therefore difficult to handle in the clinical setting. Automated analysis would reduce time and costs and therefore would make it more valuable in clinical setting.

Normative data with which DTI data of single mTBI patients can be compared, respectively, criteria which allow to decide if the DTI data of a patient predicts a negative outcome in terms of pPCS, are needed for clinical use. An example of the use of a criterion in DTI data is that of Kraus et al., who defined reduced anisotropy as 1 standard deviation (SD) below the mean FA of control subjects (Kraus et al., 2007). Another criterion to define DAI was set by Niogi et al. (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee et al., 2008). They defined DAI as FA values 2.5 SD below the region average, based on a control group with healthy adults.

The exact mechanisms that cause changes in DTI measures such as FA are still not fully understood. Authors who have looked into which specific brain regions are affected in mTBI stated future studies should examine additional brain regions and determine whether there are brain regions more susceptible to the injury (Wilde et al., 2009). More results from comparisons between DTI and neuropsychological findings respectively work status would be beneficial for clinical treatment. In general, we believe that data on impairments in daily life functioning after mTBI should be collected and considered as part of an unfavourable long-term outcome. Adequate assessment methods of daily life functioning should be defined (e.g. health questionnaires).

The relations between structural lesions in MRI / DTI and long-term outcome in mTBI patients are still controversially discussed. Longitudinal studies with larger sample sizes with objective and sufficient sampling of white matter regions are needed to better understand the relationship between brain tissue damage as measured by DTI and neuropsychological dysfunction, respectively pPCS, in patients with mTBI and to allow better assessment of the time course of DTI changes in mTBI. Such studies should ascertain whether DTI can serve as a predictive measure for an unfavourable long-term cognitive outcome after mTBI and as such can triage patients with pathological DTI imaging into rehabilitation measures.

Magnetic Resonance Spectroscopy (MRS)

Cr levels in mTBI patients were predictive of executive function and emotional distress in the study of Gasparovic et al. (2009). Their study provides preliminary evidence for the sensitivity of MRS to detect subtle disruptions in neurometabolism following mTBI and shows correlations with pPCS. Similarly, Kirov et al. found that PCS-positive patients (patients indicating at least one of the most common subacute mTBI symptoms (headache, dizziness, sleep disturbance, memory deficit or blurred vision) had lower white matter NAA than the

controls (n=12; 7.0±0.6 versus 7.9±0.5mM; p=0.0007) (Kirov et al., 2013). Global white matter NAA, therefore, showed sensitivity to the TBI sequelae associated with PCS in patients with mostly normal neuroimaging as well as GCS scores. Moreover, mTBI patients who did not report PCS were indistinguishable from controls in all markers in both tissue types (Kirov et al., 2013). The same study group previously reported in a group of 20 mTBI patients and 17 age- and gender-matched healthy controls mTBI-induced thalamic metabolite concentration changes under ±13.0% for NAA, ±13.5% for Cr and ±18.8% for Cho relative to their corresponding concentrations in the controls (Kirov et al., 2007). The authors concluded, therefore, that MRS could serve as an objective laboratory indicator for differentiating "mild" from more severe categories of TBI regardless of the presence or absence of clinical symptoms. Further studies are needed to evaluate MRS as predictive factor of pPCS or cognitive outcome.

Functional magnetic resonance imaging (fMRI)

Resting-state fMRI allows an indirect evaluation of the intrinsic neuronal activity through its metabolic and haemodynamic sequelaes providing critical insights into the pathophysiology of brain function (Messe et al., 2013). Messé et al. demonstrated PCS-specific alterations in the topological connectivity pattern following mTBI and their evolution over time (Messe et al., 2013). Other authors, however, found no significant fMRI differences after multiple sports-related concussions (Terry et al., 2012). These authors explained the lack of long-term fMRI differences with the relative plasticity of younger adults' cognitive abilities following mTBI.

Conclusions

From the evaluated diagnostic approaches to predict pPCS after mTBI, DTI, SWI, MRS and fMRI (resting-state condition) seem to have adequate sensitivity and specificity as predictive diagnostic tools according to the current literature. However, the number of studies to evaluate MRS and fMRI as diagnostic measures to predict pPCS is yet very small. Large longitudinal clinical trials are requested to validate the prognostic applicability and practicability in daily clinical practice. Future studies could compare different imaging modalities such as DTI versus SWI versus MRS versus fMRI in the same patient sample to compare the advantages and predictive strength of the different modalities. At present a lot of effort goes into evaluation of diagnostic measures in mTBI, we hope research about therapeutic measures for mTBI patients will soon grow too.

2.4. Paper 2: Central nervous system microbleeds in the acute phase predict structural integrity in the late phase after mild traumatic brain injury: a longitudinal study with a one year follow-up[2]

2.4.1. Introduction

Mild traumatic brain injury (mTBI) is with approximately 100-300 per 100'000 affected individuals per year one of the most common neurological disorders diagnosed in emergency departments (Cassidy et al., 2004; Gautschi, Frey & Zellweger, 2007). While most patients with mTBI recover within weeks to months, a subgroup continues to complain about emotional, cognitive and/or somatic symptoms, also known as post-concussion syndrome (PCS) (Carroll et al., 2004; Iverson, 2005; Ponsford et al., 2000). As testing cognitive performance several months post-injury, overall test-results often occur to be normal, several patients still complain of cognitive symptoms (Sbordone, 2001). Even after decades of mTBI research, there is an ongoing debate about the exact pathophysiology of persistent neurobehavioral and cognitive symptoms (McCrea et al., 2008). A possible explanation is that they are the consequence of diffuse axonal injury (DAI) (Bigler & Bazarian, 2010; Niogi & Mukherjee, 2010). Current research projects focus on imaging signs to contribute to the diagnosis, prognosis and understanding of the pathomechanisms of mTBI (Toth, 2015). Presence of individual patho-anatomical features on T1- or T2-weighted MR sequences, such as brain contusions and foci of haemorrhagic axonal injury do not always correlate with poor outcome after mTBI (Lee et al., 2008; Topal et al., 2008; Yuh et al., 2013). Susceptibility weighted imaging (SWI) was found to be even more sensitive in detecting traumatic lesions than CT and conventional MR (Beauchamp et al., 2011). The presence and quantity of microbleeds (MB) in mTBI patients were found to be closely related with lower scores on the Glasgow Coma Scale (GCS) on the day of trauma and on the Glasgow Outcome Scale (GOS) one year post-injury (Park et al., 2009). Diffusion Tensor Imaging (DTI) is far more sensitive to DAI than conventional MR imaging (Arfanakis et al., 2002). It allows detection of changes in the white matter tracts and brain structural connectivity (Kumar et al., 2009). Recently, researcher studied the diagnostic strength of these newer imaging modalities for PCS (Sharp & Ham, 2011; Shenton et al., 2012; Studerus-Germann, Thiran, & Daducci, A., & Gautschi, O. P., 2016; Wilde, Hunter, & Bigler, 2012) and compared cognitive status with DTI findings (Kraus et al., 2007; Kumar et al., 2009;

[2] Studerus-Germann, A. M., Engel, D. C., Bontempi, P., Thiran, J. P., Daducci, A., Romascano, D., von Ow, D., Hildebrandt, G., & Gautschi, O. P. (2016). Central nervous system microbleeds in the acute phase predict structural integrity in the late phase after mild traumatic brain injury: a longitudinal study with a one year follow-up. Manuscript submitted for publication.

Mayer et al., 2010; Messe et al., 2011; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008; Veeramuthu et al., 2015b; Wu et al., 2010). Quantitative DTI metrics, such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) represent microstructural white matter lesions that have been shown to correlate with cognitive deficits during the first months after mTBI (Kraus et al., 2007; Kumar et al., 2009; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008; Veeramuthu et al., 2015b; Wu et al., 2010). Yet, few longitudinal studies have been conducted to show how the pathophysiology of mTBI evolves over time measured with DTI (Murugavel et al., 2014; Narayana et al., 2015; Stokum et al., 2015; Veeramuthu et al., 2015a) nor with SWI (Liu, Ghimire, Pang, Wu, & Shi, 2015; Park et al., 2009; Shumskaya, Andriessen, Norris, & Vos, 2012).

The identification of patients at risk for less favourable recovery after mTBI is of paramount importance in the management of these patients. However, it is uncertain, which diagnostic instruments are reliable in clinical practice to reveal pathologies due to mTBI in the acute phase and to objectify PCS, respectively cognitive performance, in the sub-acute to late phase of mTBI. Therefore, the present study evaluated structural integrity by means of T1- and T2-weighted, SWI and DTI MR sequences in the acute phase (within one week) compared to healthy controls (CTRL) and analyzed which of the named imaging methods is sensitive to cognitive performance and PCS in the acute phase and is able to predict cognitive performance and PCS in the later phase (three and twelve months post-injury).

2.4.2. Methods

The full sample of the present study consisted of a mTBI group and a control group (CTRL). The mTBI group included patients presenting to the emergency department of the Cantonal Hospital St. Gallen between August 2012 and December 2013. Mild TBI was defined as an initial GCS of 13-15, loss of consciousness (LOC) lasting less than 30 minutes, posttraumatic amnesia (PTA) of less than 24 hours and/or any alteration in mental status at the time of injury (e.g. feeling initially confused, dazed or disoriented). Inclusion criteria were as follows: Isolated mTBI without focal neurological deficits as defined above, CT without pathological findings, age at inclusion 18-64 years and German speaking. Exclusion criteria were: Patients under the influence of alcohol (above 0.5 per mill blood alcohol), regular drug consumption, psychiatric disease under medical treatment (at present or in the last two years), previously under medical treatment for (traumatic) brain injury, recurrent falls, major concurrent injuries, residence

abroad or far away (not able to attend follow-up (FUP) meetings) and contraindication for a 3 Tesla MRI (e.g. pace maker, pregnancy). The CTRL group consisted of 20 healthy age- and sex-matched individuals recruited from the community with normal cognitive functioning. The study was approved by the local ethics Committee (EKSG 11/122). All participants provided written informed consent.

Procedure for mTBI patients

The procedures including FUP visits with neuropsychological assessment and MRI are shown in Figure 2.

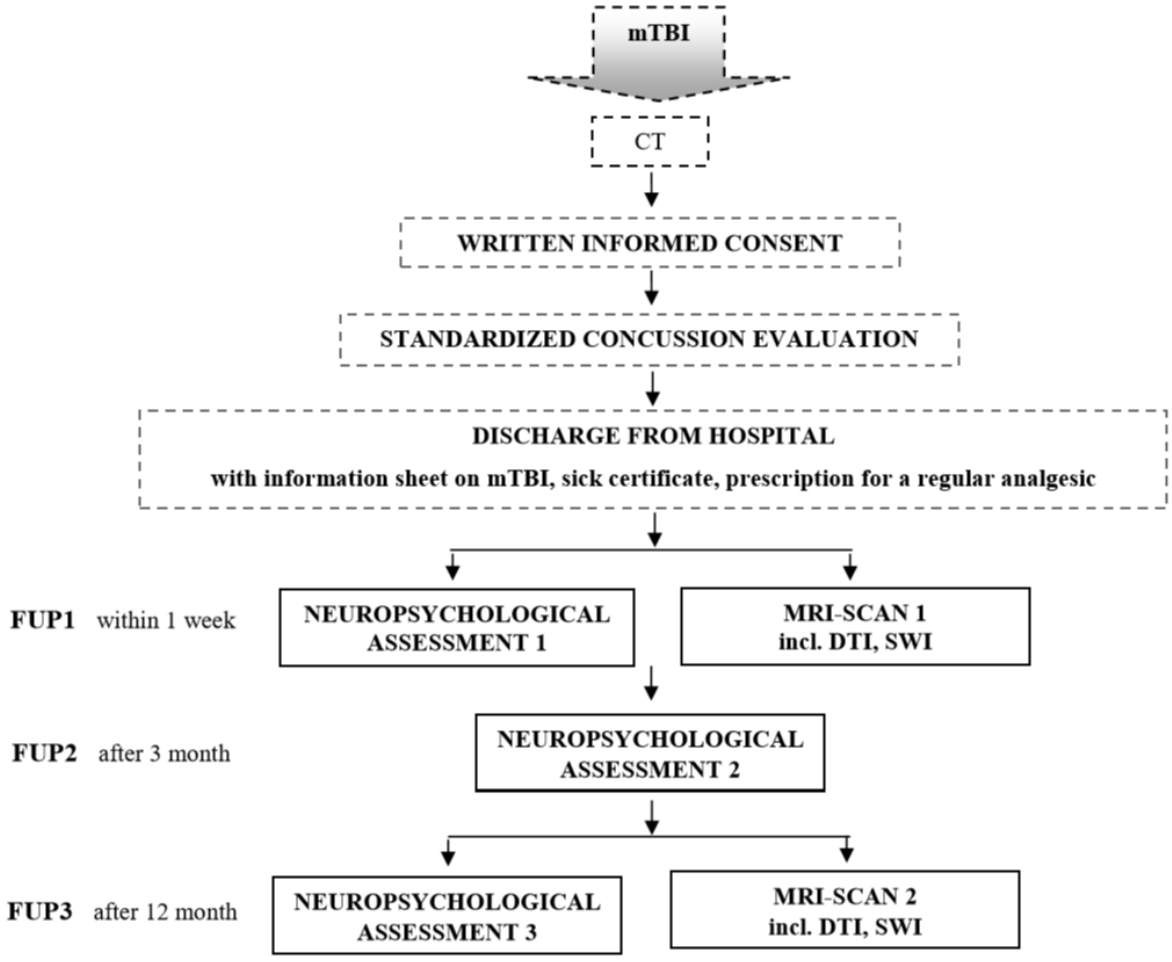


Figure 2. Flow-chart of procedures including follow-up visits.

Neuropsychological assessments (NPA)

After providing study information and collecting informed consent, the neurosurgeon on call completed a standardized concussion evaluation form, adapted according to the Acute Concussion Evaluation (ACE) form (Gioia, Collins & Isquith, 2008). Additionally, medical history, current medication, smoking habits and drug use was assessed. All 30 recruited patients

were randomly allocated to one of two study groups and received either a sick certificate for three or seven days before being discharged from hospital. As part of recommended standard care of the hospital, an information sheet on mTBI, which explains behaviour that is thought to be beneficial after mTBI, and a prescription for a regular analgesic, was handed out prior discharge.

All patients returning to FUP were assessed with a battery of validated neuropsychological measures within one week (FUP1), at three (FUP2) and twelve months (FUP3) post-injury (Table 1). The patients rated the severity of 22 concussion symptoms on a 7-point Likert scale as part of ImPACT, which was used to compute the post concussion symptom score (PCSS). Raw data, in addition to comparison, were matched to validated normative data stratified for age to transfer into one single unit (T-scores) and composite indices of attention, memory, executive function, fine motor speed and intellectual capacity. A total composite index (mean of composite indices) was calculated as a measure of overall cognitive test performance for each participant at all three time points. Information about the current job, medication and current drug consumption was also obtained at all three time points.

Table 1. Neuropsychological measures

Measured cognitive domain Measure cognitive function	**Test name / battery (reference)**
Attention	
Speed of processing / reaction time	TMT A (Reitan, 1958) Subtest Alertness from the TAP (Zimmermann and Fimm, 2002) ImPACT (Maroon et al., 2000)
Selective sustained attention	Deux Barrages (Zazzo, 1960)
Divided Attention	Subtest Divided Attention from TAP
Covert shift of attention	Subtest Covert shift of attention from TAP
Memory	
Verbal short-time memory	Subtest Digits Forward from the WIE (German version of WAIS-III; Aster et al., 2006)
Verbal working memory	Subtest Backward Span from WIE
Visual and verbal retentiveness	VVM (Schellig & Schächtele, 2001) ImPACT
Executive functions	
Verbal fluency	RWT (Aschenbrenner et al., 2000)
Design fluency	Adaption of the FPT (Regard et al., 1982) from the test-battery MNND (Balzer et al., 2011)
Cognitive processing / Interference susceptibility	German adaption of the Stroop Color and Word Test (Stroop, 1935) from the test-battery MNND (Balzer et al., 2011)
Cognitive flexibility	TMT B (Reitan, 1958)
Fine motor speed	Grooved Pegboard (Trites, 1989)
Intellectual capacity	Subtest Similarities from WIE[1]
Effort / Malingering	Green's MSVT (Green, 2004)
Psychiatric symptoms	
Post-concussion symptoms	PCSS as part of ImPACT
Depression	BDI-II (Hautzinger et al., 2006)
Anxiety	BAI (Margraf and Ehlers, 2007)
Adjustment Disorder	ANMD (Maercker et al., 2007)
Quality of life / state of health	German translation of the Health Survey SF-36 (Bullinger et al., 1995)
Stress regulation / Coping	SVF-120[2] (Janke and Erdmann, 2008)

Note. [1] This test was not performed at the second follow-up to prevent from practice effect. [2] This questionnaire was only filled in once before FUP1 since stress regulation is said to be stable. ANMD = Adjustment Disorder New Module; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; FPT = Five-Point Test; MNND = "Materialien und Normwerte für die Neuropsychologische Diagnostik" in English: materials and norm values for the neuropsychological diagnostics; MSVT = Medical Symptom Validity Test; PCSS = Post Concussion Symptom Score; RWT = "Regensburger Wortflüssigkeits-Test" in English: Regensburg word fluency test; SF = short-form; SVF = stress inventory; TAP = Test of Attentional Performance; TMT = Trail Making Test; VVM = Visual and Verbal retentiveness test; WAIS = Wechsler Adult Intelligence Scale; WIE = German version of the Wechsler Adult Intelligence Scale.

MRI data acquisition and analysis

All MR-images were acquired in the same 3T Siemens MAGNETOM Verio scanner (Siemens Medical Solutions, Malvern, PA, USA). The MRI protocol consisted of an axial 3D T1-

weighted, a fast gradient T2-weighted, a high-resolution 3D gradient-echo SWI and an axial DTI acquisition. The imaging parameters of each of those sequences are shown in Table 2.

Table 2. Imaging parameters of T1-weighted, T2-weighted, SWI and DTI acquisition

Parameters	**T1**	**T2**	**SWI**	**DTI**
TR/TE (ms)	1900/2.54	4000/107	28/20.0	8500/88
Flip angle (deg)	9	150	15	0
Slices	192	27	72	41
Slice thickness (mm)	0.90	4.0	1.8	3.0
FOV (mm^2)	230	210	210	220
Base resolution	256	512	320	128
Voxel size (mm)	0.9x0.9x0.9	0.5x0.4x4.0	0.7x0.7x1.8	1.7x1.7x3.0
Receiver bandwidth (Hz/pixel)	170	222	120	1502
Acquisition type (dimensions)	3	2	3	2
Specific parameters depending on sequence				64 diffusion directions with b-value = 1000 s/mm^2 and 1 image with b-value = 0 s/mm^2 Matrix size: 128x128

Note. SWI = Susceptibility weighted image, DTI = Diffusion tensor imaging, FOV = Field-of-View, TR = Repetition Time, TE = Echo Time.

Analysis of T1-weighted, fast gradient T2-weighted and SWI sequences

The neuroradiologist in charge screened the MR images for MB (counted their amount and reported their localisation), as well as for other findings such as contusion, haematoma, oedema or incidental findings. Group differences regarding neuropsychological test results and PCSS were calculated between mTBI with MR findings potentially caused by mTBI (including MB, contusion, haematoma or oedema) and mTBI without such MR findings, as well as between mTBI with MB and such without MB to evaluate if pathophysiological findings relate to neuropsychological outcome. Additionally correlations between the number of MB and cognitive performance and symptoms of PCS were calculated.

Analysis of DTI data

Semi-automated methods from the FSL toolbox have been used to allow investigating the whole brain without the need of manual segmentation of regions of interest (ROI) (Smith et al., 2004). First, Eddy Current and Linear Motion Correction were performed by aligning all the diffusion-

weight image (DWI) volumes to the image without diffusion-weighting using 12 degrees of freedom. The brain was segmented using the brain extraction tool (BET) and the tensor model was fit in every voxel with the DTIFIT program to estimate fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps (Smith, 2002). Voxelwise statistical analysis of the DTI derived maps was carried out using tract-based spatial statistics (TBSS) (Smith et al., 2006). All subjects' FA maps were non-linearly aligned into a common space (FSL's FMRIB58_FA template) using the registration tool FNIRT ("Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2,"; Andersson, Jenkinson, & Smith, 2007; Rueckert et al., 1999). Thereafter, the mean FA image was created and thinned to create a mean FA skeleton that represents the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. A skeleton threshold of 0.2 was used. The same procedure was applied to MD, AD and RD maps. For group comparison, randomise tests on skeletonized DTI images were conducted with threshold-free cluster enhancement (TFCE) option and 10000 permutations. Statistical results were generated with the family-wise error (FWE) correction for multiple comparisons. In addition, a voxel-based morphometry (VBM)-like analysis of the DTI maps was performed (VBM-DTI). Whole brain FA, MD, AD and RD maps were registered to the FMRIB58_FA template, smoothed with a Gaussian kernel of sigma = 3mm and then fed into RANDOMISE.

Randomise step: Voxelwise general linear model (GLM) was designed with age and sex as covariates. We tested for differences in DTI parameters between patients at FUP1 and controls, between patients at FUP3 and controls as well as differences between mTBI at FUP3 and mTBI at FUP1. The resulting t-stat FWE corrected maps were then set at a threshold with a significance level alpha = 0.05.

Region by region analysis: FA, MD, AD and RD values in significant voxels were extracted to compute their correlation with clinical data. Furthermore, a slightly modified version of the MNI structural brain atlas, included in the FSL package, was used to identify the brain areas with TBSS and VBM-DTI differences and to compute mean FA, MD, AD and RD in such regions.

Statistical analysis

Statistical analysis was conducted using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA). Group comparisons were performed using unpaired, two-tailed Student’s t-tests or Mann-Whitney U test. To evaluate the relationship between two categorical variables, Pearson’s chi-squared test

(X^2), respectively Fisher's exact test, were used. Correlations were calculated with Pearson or Spearman correlation. P values < 0.05 were considered statistically significant.

2.4.3. Results

The full sample of the present study consisted of 50 participants: 30 mTBI patients (mean age: 35.0, SD: 13.4, range: 18-55 years, 16 males and 14 females) and 20 healthy controls (mean age: 43.2, SD: 14.4, range: 19-62 years, 10 males and 10 females). Complete MRI data were available for 30 mTBI patients (DTI data for 29) at FUP 1 and for 20 mTBI patients (DTI data for 18) at FUP 3. The MR data of one healthy control was excluded due to poor image quality. There were no group differences between mTBI patients and controls regarding sex, age, years of education and handedness at FUP1 or FUP3 (Table 3).

Table 3. Demographics of scanned healthy controls versus mTBI patients at FUP1 and FUP3

Parameter	Healthy Controls	mTBI patients FUP1	p value	mTBI patients FUP3	p value
Age (years), M (SD)	42.21 (14.07)	34.97 (13.38)	0.077	36.33 (12.82)	0.175
Gender			0.684		0.752
Male	9	16		11	
Female	10	14		10	
Education (years), M (SD)	13.58 (1.77)	12.66 (2.52)	0.177	13.00 (2.58)	0.419
Handedness			0.273		0.488
Right	19	27		19	
Left	0	3		2	
Total	n=19	n=30		n=21	

A complete NPA including PCSS could be performed with 27 patients within one week (FUP1), 24 at three months (FUP2) and 20 at one year (FUP3) post-injury. The neuropsychological data of one patient was excluded since he failed in the MSVT screening for bad effort or malingering at all neuropsychological FUPs. No other participant failed in the MSVT, hence it can be assumed that all other subjects showed sufficient personal effort during cognitive testing. Dropouts were due to motivational reasons of the patients. Times of FUPs (in days) were as follows: FUP1: MRI 1 / NPA 1 range: 0-7, MD: 2.7, SD: 1.8), FUP2: NPA 2 (range: 81-123 days, MD: 95.9, SD: 9.2) and FUP3: MRI 2 / NPA 3 (range: 355-406 days, MD: 372.8, SD: 13.0).

The MR findings of mTBI patients from FUP1 and FUP3 as well as from healthy controls are shown in Table 4. At FUP1, one third of the mTBI sample (10 out of 30) showed MR findings possibly associated with the mTBI (MB, contusion, haematoma or oedema), while two thirds (20 out of 30) did not show a mTBI-associated MR finding.

Table 4. MRI findings of mTBI-patients at FUP1 and FUP3 versus healthy controls

	FUP1		**FUP3**		**Healthy controls**	
Number of patients / healthy controls with:	Frequency	Per cent	Frequency	Per cent	Frequency	Per cent
No cerebral MRI findings :	14	46,7	14	80,0	9	45,0
Cerebral MRI findings[2]:	16	53,3	6	35,0	11	55,0
Haemosiderin deposit / Microbleeds[1]	4	13,3	4	20,0	5	25,0
Contusion[1]	1	3,3	0	0	0	0
Haematoma[1]:	8	26,7	0	0	0	0
Subdural haematoma[1]	2	6,7	0	0	0	0
Epidural haematoma[1]	1	3,3	0	0	0	0
Preseptal/supraorbital haematoma[1]	1	3,3	0	0	0	0
Subgaleal haematoma[1]	4	13,3	0	0	0	0
Subarachnoid haematoma [1]	2	6,7	0	0	0	0
Oedema[1]	2	6,7	0	0	0	0
Foci of gliosis	5	16,7	2	9,1	6	30,0
Calcifications	3	10,0	1	4,5	3	15,0
Moderat cerebral atrophy	1	3,3	0	0,0	0	0,0
Unclear malformations	0	0	0	0	2	10,0
Total patients	30	100,0	20	100,0	20	100,0

Note. [1] Microbleeds, contusion, haematoma, oedema in mTBI patients were associated with the mTBI. [2] at FUP1: 1 patient with MRI finding had just one type of MRI finding, all other had more than one type of MRI finding.

The number and regional distribution of MB in mTBI patients at FUP1 and FUP3 are shown in Table 5. At FUP3, MB were the only MR finding possibly associable to the mTBI in 20% of the patients (4 out of 20). In two patients, MB were only found at FUP3, one of them reported that he had suffered a second mTBI four months after the initial mTBI, which could account for the new MB, while the possible origin of the new MB in the other patient was not known. It is noteworthy that haemosiderin deposits were found in five out of 19 healthy controls (26.3%) as an incidental finding, the neuroradiologist associated two of them with calcification, one with microangiopathy and two were labelled as possible MB, possibly due to unknown degenerative disease.

Table 5. Number and localisation of Microbleeds (MB) at FUP1 and FUP3

			Localisation of MB: FUP1/FUP3						
Sex	Age (y.)	Number of MB	Frontal lobe	Temporal lobe	Parietal lobe	Occipital lobe	Brainstem	Cerebellum	Corpus callosum
M	52	<5	x/-	0/-	0/-	0/-	0/-	0/-	0/-
M	50	5-20	x/x	0/x	0/0	0/0	x/x	x/x	x/x
F	48	>20	x/x	x/x	x/x	x/x	0/0	0/0	0/0
M	20	5-20	x/-	x/-	0/-	x/-	0/-	0/-	0/-
F	26	5-20	0/0	0/0	-/x	0/0	0/0	0/0	0/0
M	39	5-20	0/x	0/0	-/-	0/0	0/0	0/0	0/0

Note. Areas with MB are marked with x, areas with no microbleeds are marked 0 and missing data due to drop-out is marked with -.

Table 6 shows the regions with significant group differences for the DTI-parameters FA, AD, RD and MD between mTBI patients at FUP1 and controls, between patients at FUP3 and controls as well as differences between patients at FUP3 and patients at FUP1.

Table 6. Significant group differences between controls (CTRL) and mTBI patients at FUP1 and FUP3, respectively mTBI patients at FUP1 and FUP3 in DTI parameters

Technique	Image type	CTRL *vs* mTBI at FUP1	CTRL *vs* mTBI at FUP3	Regions with significant group differences	mTBI at FUP1 *vs* mTBI at FUP3	Regions with significant group differences
TBSS	**FA**	no differences	CTRL<mTBI	Right: white mater	no differences	
	AD	no differences	no differences		mTB at FUP1> mTBI at FUP3	Bilaterally: in white matter, parietal & occipital lobe
	RD	no differences	CTRL> mTBI	Bilaterally: in white mater, frontal, parietal, temporal & occipital lobe, Right: caudate nucleus, putamen, thalamus	no differences	
	MD	no differences	CTRL> mTBI	Bilaterally: in frontal, parietal, temporal & occipital lobe, caudate nucleus, putamen, white mater	no differences	
VBM-DTI	**FA**	no differences	CTRL< mTBI	Left: parietal lobe	mTB at FUP1> mTBI at FUP3	Bilaterally: in white matter, thalamus, Left: caudate nucleus
	AD	no differences	CTRL> mTBI	Bilaterally: in white mater	mTB at FUP1> mTBI at FUP3	Bilaterally: white matter, parietal, temporal & occipital lobe, insula, Left: frontal lobe, putamen
	RD	no differences	CTRL> mTBI	Bilaterally: in white mater, Right: frontal, parietal & temporal lobe	no differences	
	MD	no differences	CTRL> mTBI	Bilaterally: in white mater, Right: frontal, parietal & temporal lobe	mTB at FUP1> mTBI at FUP3	Bilaterally: white matter, Left: frontal, parietal and occipital lobe

Note. TBSS = Tract-based spatial statistics, VBM-DTI = Voxel based morphometry (on DTI data), FA = fractional anisotropy, AD = axial diffusivity, MD = mean diffusivity, RD = radial diffusivity, vs = versus

MR findings from FUP1: group comparisons and correlations with NPA

The group of mTBI patients with MR findings possibly associated with the mTBI (n=10) and the group without MR findings (n=20) did differ significantly in some symptom values measured with the PCSS at all three times of FUP – in all of them mTBI patients with MR findings showed higher symptom values than mTBI without MR findings (see Table 7).

Table 7. Significant group differences between patients with versus patients without MRI findings at FUP1 in PCSS at FUP1-FUP3

FUP1				
	mTBI with MRI findings M (SD)	**mTBI without MRI findings M (SD)**	***U***	***p***
Feeling slowed down	3.00 (1.51)	1.35 (1.94)	32.00	0.037
Difficulty remembering	3.00 (1.60)	1.00 (1.80)	27.00	0.016
FUP2				
Difficulty concentrating	3.00 (1.00)	0.13 (0.50)	0.50	0.002
FUP3				
Difficulty concentrating	1.29 (1.70)	0.17 (0.58)	0.50	0.002

Mild TBI patients with MR findings did not differ significantly in any of the cognitive tests or psychological questionnaires compared to mTBI patients without MR findings from all three times of FUP. The group comparison between mTBI patients with MB (MB 1) compared to mTBI patients without MB (MB 0) as measured at FUP1 showed significant group differences in eight neuropsychological test results at FUP1 (five of them measuring psychomotor speed and speed of information processing), in one test result at FUP2 and in five test results at FUP3, as can be seen in Table 8. In all expect one of the test scores with significant group differences, MB 1 performed worse than MB 0. The only test score wherein the MB 1 group showed a better performance at FUP1 than the MB 0 group was the reaction time composite score of the test battery ImPACT. Regarding PCSS, significant group differences between MB 1 and MB 0 were only found in the FUP3. The MB 1 group showed higher symptom values in total symptom score, fatigue, difficulty concentrating and difficulty remembering at FUP3 than the MB 0 group (see Table 8 for details).

Table 8. Significant group differences between mTBI-patients with microbleeds (MB 1) versus without microbleeds (MB 0) at FUP1 in neuropsychological assessment (NPA) including PCSS from FUP1-FUP3

Tested cognitive skill (units) - test name	**MB1** **M (SD)**	**MB0** **M (SD)**	***U***	***p***
FUP1				
Verbal fluency lexical (words per min.) - RWT	6.33 (0.58)	14.55 (5.04)	5.00	0.014
Verbal fluency categorical (words per min.) - RWT	17.00 (2.65)	23.73 (6.26)	7.00	0.027
Design fluency (items per 3 min.) - Design Fluency MNND	22.67 (3.51)	33.13 (7.99)	7.00	0.024
Fine motor speed dominant hand (sec. till completion) – Grooved Pegboard	93.67 (22.50)	63.05 (7.91)	4.50	0.011
Fine motor speed non-dominant hand (sec. till completion) – Grooved Pegboard	90.67 (16.65)	72.19 (10.86)	7.50	0.031
Delayed verbal recall (number of recalled items) - VVM	3.67 (2.89)	9.87 (5.51)	9.00	0.041
BDI-II severity coding (1=minimal, 2= mild, 3= median, 4 = sever depressive symptom) – BDI-II	1.33 (0.578)	0.30 (0.56)	7.50	0.024
Reaction time composite score (T-score) - ImPACT	51.33 (5.13)	43.09 (6.26)	9.50	0.046
FUP2				
Divided attention visual cue (mean reaction time in sec.) - TAP	827.00 (43.14)	724.85 (74.46)	7.00	0.035
FUP3				
Extrinsic alertness (mean reaction time in sec.) - TAP	241.50 (0.71)	219.53 (15.45)	2.00	0.047
Speed of processing (sec. till completion) - TMT A	25.50 (0.71)	16.71 (4.44)	2.00	0.047
Immediate verbal recall (number of recalled items) - VVM	9.50 (0.71)	15.53 (3.81)	2.00	0.047
Fine motor speed dominant hand (sec. till completion) - Grooved Pegboard	74.50 (9.19)	55.76 (4.80)	0.00	0.012
Composite score attention (T-score) - mean of all tests measuring attention	46.50 (1.56)	52.14 (2.38)	0.00	0.012
PCSS[1] **:**				
Total Symptom Score	12.29 (12.87)	5.00 (4.24)	1.50	0.023
Fatigue	1.86 (1.95)	0.58 (1.17)	1.50	0.023
Difficulty concentrating	1.29 (0.70)	0.17 (0.58)	0.00	0.012
Difficulty remembering	1.71 (2.22)	0.00 (0.00)	0.00	0.012

Note. Lower values indicate better performance in the following tests: Grooved Pegboard, BDI-II, TAP, TMT A, PCSS. Higher values indicate better performance in the following tests / composite scores: RWT, Design Fluency MNND, VVM, ImPACT, overall performance for the domain attention. [1] A higher score reflects a higher symptom severity (per symptom six was the highest selectable value, zero means the patient does not experience a symptom).

Additionally, in the group of patients with MB (n=4), there were significant correlations between the number of MB at FUP1 and three test scores from the NPA at FUP1, one test score from the NPA at FUP2 and four test scores from the NPA at FUP3, as can be seen in Table 9.

Table 9. Significant correlations between number of MB from FUP1 and performance on neuropsychological tests, respectively symptom severity in PCSS at FUP1-FUP3 in the group of patients with MB (n=4)

Tested cognitive skill or symptom - test name	***R***	***p***
FUP1		
Word fluency lexical - RWT	-0.482	0.015
Word fluency semantic - RWT	-0.398	0.049
BDI-II severity coding - BDI-II	0.523	0.006
FUP2		
BDI-II severity coding– BDI-II	0.459	0.032
PCSS :		
Total Symptom Score	0.477	0.025
Nausea	0.500	0.018
Dizziness	0.535	0.010
Sensitivity to noise	0.835	0.000
Sleeping more than usual	0.425	0.049
Feeling more emotional	0.474	0.026
Sadness	0.474	0.026
Nervousness	0.724	0.000
Difficulty concentrating	0.513	0.015
Difficulty remembering	0.560	0.007
FUP3		
Speed of processing - TMT A	-0.517	0.028
Fine motor speed dominant hand - Grooved Pegboard	-0.584	0.011
Composite score attention – overall performance for the domain attention	-0.547	0.019
BDI-II severity coding– BDI-II	0.728	0.001
PCSS :		
Total Symptom Score – PCSS	0.504	0.033
Nausea	0.500	0.035
visual problems	0.728	0.001
Fatigue	0.570	0.013
Difficulty concentrating	0.841	0.000
Difficulty remembering	0.835	0.000

All significant correlations between number of MB and cognitive tests were negative, which means that more MB were associated with worse performance in the cognitive tests. The number of MB from FUP1 correlated significantly with ten symptom values of the PCSS at FUP2 and with six symptom values of the PCSS at FUP3 (Table 8) – all correlations were positive, which suggests that more MB were associated with higher symptom severity.

Furthermore, TBSS and VBM-DTI analyses revealed no significant differences in diffusion parameters between mTBI patients at FUP1 and controls, due to the missing detection of abnormalities by means of DTI, no correlations between DTI parameters and neuropsychological outcome were calculated.

MRI findings from FUP3: Group comparisons and correlations with NPA

Group comparisons between mTBI patients with MB (n=4; representing the total of MR findings) and mTBI patients without MB (n=16) as reported from the MR scan at FUP3 showed a significant difference in the value of the symptom "difficulty concentrating" of the PCSS at FUP3 (U=0.50, p=0.002). Patients with MB named higher values in the symptom "difficulty concentrating" (M: 3.00, SD: 1.00) than patients without MB (M: 0.13, SD: 0.50). There were no differences between patients with versus without MB regarding cognitive test results, nor in DTI parameters calculated with VBM-DTI. Patients with MB showed significantly higher values in the following DTI parameters of TBSS compared to patients without MB: MD in left parietal lobe (t=2.35, p=0.032) and in right temporal lobe (t=2.32, p=0.034) and RD in right occipital lobe (t=2.53, p=0.022).

TBSS and VBM-DTI analysis both showed significant differences in FA, RD and MD between mTBI patients at FUP3 (twelve months post-injury) and controls with the mTBI patients having higher values in FA and lower values in MD and RD, compared to the controls in widespread regions (see Table 6). Additionally, the VBM-DTI analysis revealed significantly lower values in AD for the mTBI group at FUP3 compared to the controls.

There were significant correlations between the number of MB at FUP3 and the following symptoms of PCSS: *"*Difficulty concentrating" (R=0.875, p=0.000), *"*Difficulty remembering" (R=0.682, p=0.001) and *"*visual problems" (R=0.610, p=0.006). More MB correlated with higher symptom severity at FUP3. A significant correlation was also found between the number of MB from FUP3 and the composite score attention (R=-0.471, p=0.042), as well as BDI-II

severity coding (R=0.610, p=0.006) from FUP3. The number of MB correlated positively with twelve DTI parameters (MD and RD from several areas as can be seen in Table 10) from TBSS, respectively with four DTI parameters (AD, MD and RD in white matter) from VBM-DTI.

Table 10. Significant correlations between number of Microbleeds and DTI parameters from FUP3

Technique	DTI parameter	Area	Cerebral hemisphere	R	P
TBSS	MD	frontal lobe	L	0.540	0.021
		occipital lobe	R	0.607	0.008
			L	0.574	0.013
		parietal lobe	R	0.612	0.007
			L	0.684	0.002
		temporal lobe	L	0.552	0.017
		white matter	R	0.502	0.034
			L	0.573	0.013
	RD	occipital lobe	R	0.687	0.002
		parietal lobe	R	0.672	0.002
		white matter	R	0.498	0.036
			L	0.528	0.024
VBM-DTI	AD	white matter	L	0.474	0.047
	MD		R	0.495	0.037
			L	0.622	0.006
	RD		L	0.611	0.007

Note. TBSS = Tract-based spatial statistics, VBM-DTI = Voxel based morphometry (on DTI data), AD = axial diffusivity, MD = mean diffusivity, RD = radial diffusivity, L = left, R = right.

Longitudinal analysis of MR findings in mTBI patients: FUP1 versus FUP3

When comparing only the subset of 20 patients, which were scanned twice the number of MR findings associated with the mTBI at FUP1 (sum of MR findings=10) was by trend higher than the number of MR findings at FUP3 (sum=4, Wilcoxon-test=-1. 51, p=0.132). The number of MB did not differ significantly between FUP1 (sum of MB=34) and FUP3 (sum=38, Wilcoxon-test=-1.41, p=0.157). Figure 3 shows the significant differences in DTI parameters between the acute phase and the late phase in mTBI-patients. The TBSS analysis showed greater AD values in the acute phase (FUP1) compared to the late phase (FUP3) post-injury in the group of mTBI

patients. The VBM-DTI technique revealed consistently significantly higher values in FA, MD and AD in several areas in the acute phase compared to the late phase.

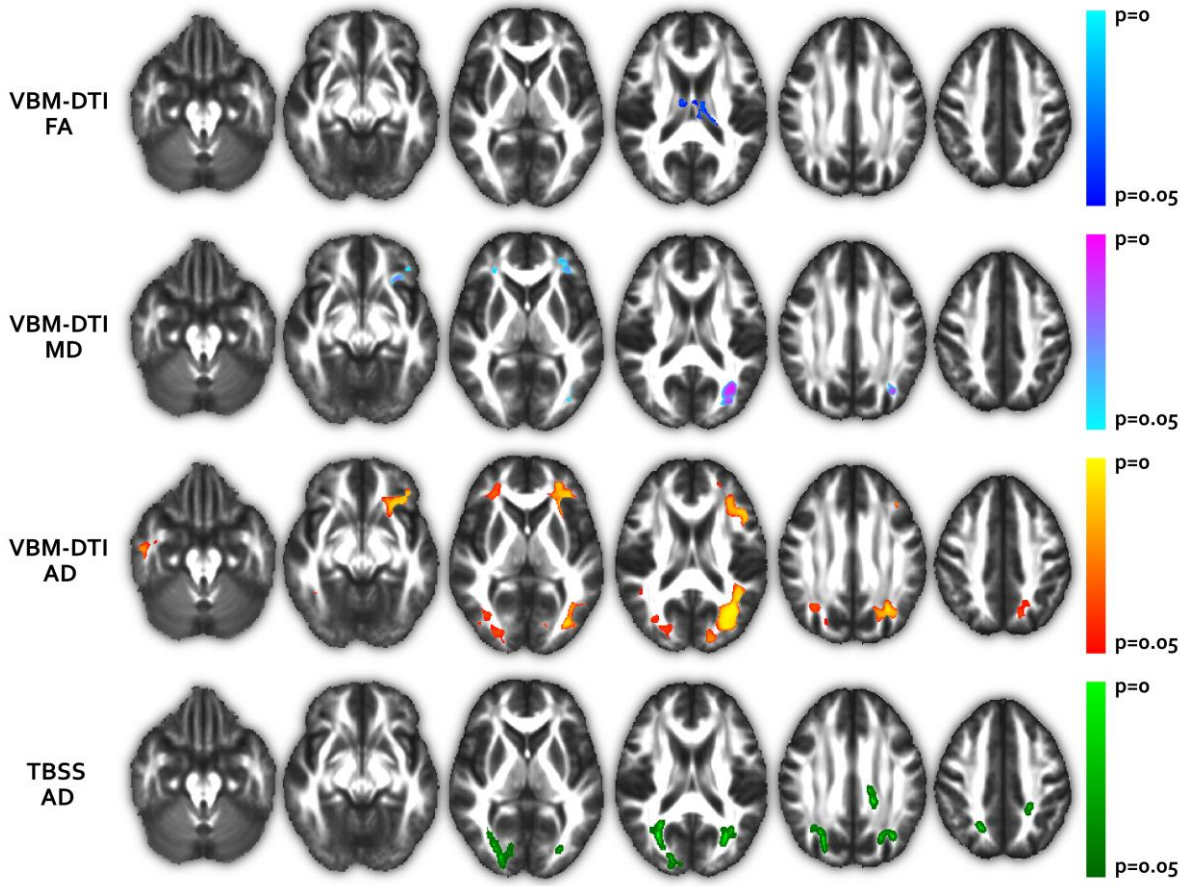


Figure 3. VBM-DTI and TBSS findings in the acute phase versus late phase in mTBI-patients

Note. VBM = Voxel-based morphometry and TBSS = tract-based spacial statistics findings in the acute phase versus late phase in mTBI patients. Blue, turquoise and yellow areas show where VBM-DTI = Voxel based morphometry (on DTI data) revealed higher values of FA = fractional anisotropy, MD = mean diffusivity and AD = axial diffusivity respectively, in the acute phase (1st to 3rd row). Green clusters identify areas where TBSS revealed higher values of AD in the acute phase (last row).

2.4.4. Discussion

Our findings show that mTBI patients with a negative CT and possible trauma-related abnormalities on MR in the acute state, have more cognitive symptoms such as slowing, difficulty in memory and concentration than mTBI patients without abnormal MR findings in the acute and chronic phases. This supports previous findings showing an association between MR abnormalities and acute symptoms, suggesting the prognostic value of MR abnormalities for persistent symptoms (Yuh et al., 2013). MB measured with SWI could be considered sensitive to acute cognitive performance and as a prognostic factor for cognitive outcome and

persistent PCS in mTBI patients since they may lead to damage to neuronal and vascular tissue in accordance with findings from Huang et al. (Huang et al., 2015). Our findings of correlations between the number of MB and higher symptom severity are in line with previous findings, which showed relations between the presence and quantity of MB and lower scores on the GOS one year post-injury (Park et al., 2009). Additionally, they are in line with findings from Liu et al. showing significant higher numbers of MB in patients with PCS compared to patients without PCS. However, we could not find a significant difference in the quantity of MB between patients with PCS compared to patients without PCS and we are not able to conclude from our data that MB decrease over time like they showed (Liu et al., 2015).

As far as we know, no other currently published study has shown correlations between MB, as measured with SWI, and cognitive performance in mTBI patients. There is a study showing that higher lesion volume for SWI was associated with poorer memory and processing speed impairment. Spitz et al. did not explain exactly what type of lesions were analysed as lesion volume (Spitz et al., 2013). We assume that the lesion volume reflects at least partially MB and therefore our findings are in line with their results. Differences in cognitive performance in the acute phase in patients with MB were most commonly found in cognitive tests measuring psychomotor speed and speed of information processing, which is in line with findings of Shumskaya et al. (2012).

Evidence exists that MB are often seen in stroke patients as well as in some of our current asymptomatic control patients, the specificity of MB for mTBI is questionable (Akoudad et al., 2014; Huang et al., 2015; Kim & Lee, 2015). Nevertheless, it seems probable that MB, regardless of their origin, are a potential risk factor for worse neuropsychological performance and outcome and therefore further investigations in both mTBI, other diseases and healthy controls are necessary.

In the present study, correlations between higher numbers of MB and higher values in the DTI parameters MD, AD and RD were found, which could be explained by the structural damage to the tissue induced by the MB, which leads to weaker constraining of water molecule movements, more freely moving water and therefore higher values of MD, AD and RD. The latter correlations, however, are not clinically operational at this moment, due to the complexity of DTI analyses and present lack of concordance with clinical findings. DTI patterns in mTBI patients over time are explained further by our results. In the acute phase, we did not find a

significant difference in DTI patterns of mTBI patients scanned within one week compared to healthy controls. Interestingly after twelve months, higher values in FA and lower values in MD, RD, as analysed with TBSS and VBM-DTI, as well as in AD (as analysed with VBM-DTI only) compared to healthy controls were found in widespread regions, possibly reflecting axonal degeneration. Therefore, late DTI measurements could possibly be used as proof of past mTBI for insurance reasons. In the TBSS analysis, no differences were found in AD for the late phase after mTBI compared to controls, which is in accordance with the finding of Messè et al., who did not find group differences in AD neither for the subacute (8-21 days) nor the late phase (six months) post-injury (Messe et al., 2011). To the best of our knowledge, there are no other studies showing comparable one-year post mTBI DTI data.

The longitudinal comparison between DTI parameters in the group of mTBI patients revealed higher values in FA, MD and AD with VBM-DTI, respectively in AD only with TBSS in the acute phase (within one week post-injury) compared to the late phase (after twelve months) post-injury in several areas. Higher FA in mTBI has been related to an inflammatory response such as axonal swelling or cytotoxic oedema (Bazarian et al., 2007; Chu et al., 2010; Mayer et al., 2010). Our pattern of higher values in FA in the acute phase compared to the late phase in the same patients with mTBI resembles the finding of Veeramuthu et al., which also found higher values in FA in their mTBI group in the acute phase (within 24 hours) compared to a late phase (after six months) (Veeramuthu et al., 2015b). Our pattern of significantly higher MD and AD in the acute phase compared to the late phase, after twelve months, in the same group of mTBI patients is a new finding, since other studies comparing mTBI at a similar time point did not find significant group differences in MD or AD (Narayana et al., 2015; Stokum et al., 2015; Veeramuthu et al., 2015b). Additionally it calls for further investigations comparing diffusion parameters between mTBI patients in the acute and late phase.

There is an ongoing discussion regarding the best methodological approach for the analysis of DTI data and our results show different findings for the data analyzed with TBSS versus VBM. It is worth mentioning that, analysing data with a TBSS-like pipeline, gives as output all the DTI derived images (and not yet skeletonized) aligned to the FSL's FMRIB58_FA template. It is then straightforward to perform a VBM-like analysis on DTI-derived maps (FA, MD, AD and RD). Given the ongoing debate on the TBSS versus VBM-like analysis of DTI data, we decided to take an unbiased approach and perform both of them. The randomisation step, lasting for a few days for each run on a modern multi-core desktop PC, was the only time-consuming

part of the VBM-like processing of DTI data. Additionally, the used acquisition parameters between DTI studies vary and alterations in acquisition factors have shown alterations in FA, MD, AD and RD, e.g. our study used 64 diffusion directions. This is more than most studies comparing mTBI with healthy controls used. Since literature has shown that more diffusion directions lead to more accurate estimation of the diffusion tensor (Barrio-Arranz, Luis-Garcia, Tristan-Vega, Martin-Fernandez, & Aja-Fernandez, 2015) the choice to use 64 directions is valid. Despite all efforts, numerous factors influence the validity in the comparison of DTI results; e.g. selection of mTBI patients (especially with or without CT findings), type of scanner, scan parameters, time of scan post-injury and type of analysis method (e.g. TBSS or VBM-DTI).

Although the current findings are not instantly convertible to everyday clinical use, it does once again show that mTBI goes beyond being an acute disease. Chronic pathophysiological pathways are triggered leading to DTI changes at a later stage as shown in the current study and by Yuh et al. (Yuh et al., 2014). As the disconnection is not present, or at least not detectable in the acute phase compared to controls, it is probable that a chronic process leads to destruction of neuronal pathways and forming of gliosis as seen in all peripheral and central nerve injuries. The theory that MB release iron increasingly into the tissue and thereby leading to further destruction, possibly leading to triggering inflammatory pathways as well is still to be proven ("Deferoxamine reduces intracerebral hematoma-induced iron accumulation and neuronal death in piglets,"; "Quantification of iron in the non-human primate brain with diffusion-weighted magnetic resonance imaging").

Limitations

Our findings are limited by the small sample size, which was initially anticipated differently and was primarily due to lack of patient motivation to participate, in spite of active telephone follow-ups and reimbursement of travel costs and relatively strict inclusion criteria. The small group of patients with MB make our findings of MB as a predictive marker of neuropsychological outcome critical. Therefore it should be rather seen as a trend, which needs further validation by studies with bigger sample sizes. Due to the lack of NPA of the healthy control group we were not able to analyse the neuropsychological effects of MB in absence of mTBI.

Conclusions

Structural integrity measured by DTI is more affected by mTBI in the late phase than in the acute phase, since structural reorganizing processes only start after the acute phase. In the acute phase SWI seems to be an appropriate measure to detect neuropsychological deficits. SWI can be considered as a prognostic factor for cognitive outcome and PCS in mTBI patients. We recommend conducting an MRI including SWI sequences if a patients' recovery seems to develop unfavourably within the first few weeks after mTBI, to give a recommendation for coaching by a therapist (neuropsychologist, psychotherapist or occupational therapist) is necessary.

2.5. Paper 3: Three versus seven days to return to work after mild traumatic brain injury: a randomised parallel-group trial with neuropsychological assessment[3]

2.5.1. Introduction

Approximately 100 to 300 per 100'000 individuals sustain a mild traumatic brain injury (mTBI) per year (Cassidy et al., 2004). Although most patients with mTBI recover within days to weeks, some patients experience persistent physical, cognitive or behavioural symptoms, often referred as post-concussion syndrome (PCS) (Ryan & Warden, 2003). The estimated prevalence of PCS varies widely, with 20 to 50% of mTBI patients reporting symptoms beyond three months and more than 10% still after one year (Faux, Sheedy, Delaney, & Riopelle, 2011; von Wild, K R H, 2008). Persisting symptoms can include post-traumatic headache, sleep disturbance, fatigue, cognitive impairment, balance disorders, dizziness and affective disorders (Iverson, 2005). Persistent subjective cognitive complaints may disrupt the patients' social relationships and their ability to resume leisure and work-related activities (van der Naalt, 2001; Yang, Tu, Hua, & Huang, 2007).

While the exact pathophysiology of cognitive impairment after mTBI is still unclear (Giza & Hovda, 2014), it is generally accepted that functioning is most compromised for the first week after trauma (Studerus-Germann et al., 2016). During this period and beyond the brain is exceedingly vulnerable for further damage (Giza & Hovda, 2001, 2014; Iverson, 2005; McCrea et al., 2003; Silverberg & Iverson, 2013). Strenuous cognitive and physical activities have been shown to exacerbate symptoms and thereby delay recovery (McCrory, Makdissi, Davis, & Collie, 2005). Thus, current recommendations for mTBI patients generally include relative rest for the first two to five days without physical or cognitive exertion. However, bed-rest beyond the nightly sleep is generally not advised and patients are encouraged to resume normal activities as soon as possible (Guskiewicz et al., 2004; Silverberg & Iverson, 2013).

The scientific evidence for recommendations for return-to-work (RTW) or resume activities of daily living (ADL) after mTBI is weak and varies greatly between one and 30 days (Kruijk et al., 2001). Despite an overall high incidence of mTBI and PCS, no randomised trial has so far compared the duration of sick leave after mTBI and its impact on the incidence of PCS and

[3]Studerus-Germann, A. M., Engel, D. C., Stienen, M. N., von Ow, D., Hildebrandt, G., & Gautschi, O. P. (2016) Three versus seven days to return-to-work after mild traumatic brain injury: a randomised parallel-group trial with neuropsychological assessment. Manuscript submitted for publication.

subsequent cognitive outcome. The goal of this study was, therefore, to evaluate if the recommendation of a short (= three days) or intermediate (= seven days) time to RTW leads to a more favourable outcome regarding PCS and neuropsychological performance up to twelve months after mTBI and to evaluate the influence of the effective time to RTW on PCS and cognitive outcome.

2.5.2. Materials and Methods

Consecutive mTBI patients from 18 to 64 years without focal neurological deficits presenting to the emergency department of the Cantonal Hospital of St.Gallen, Switzerland, were screened to participate in a single-centre prospective, randomised, parallel-group trial between August 2012 and December 2013. The study was approved by the local ethics committee (EKSG 11/122). All patients gave written informed consent prior to study inclusion. Mild TBI was defined with an initial Glasgow Coma Scale (GCS) of 13 to 15 at scene with loss of consciousness (LOC) lasting < 30 minutes and/or posttraumatic amnesia (PTA) < 24 hours. Computed tomography (CT) had to prove absence of pathological intracranial findings. Exclusion criteria included alcoholization (above 0.5 per mill blood alcohol), regular drug consumption, known psychiatric or neurological disease, previous (traumatic) brain injury, homelessness (due to the difficulty to contact patients for the scheduled follow-ups) and residence abroad, as well as major concurrent injuries.

After comprehensive study information and written informed consent, the neurosurgeon on call performed a physical baseline examination and completed a standardized concussion evaluation form (Gioia et al., 2008). All recruited patients were randomly allocated to one of two study groups and received either a sick certificate for three days (3D-group) or seven days (7D-group) before being discharged from hospital. Previous to the start of recruitment, a list was generated with a random order of numbers corresponding to the two durations of sick leave and the neurosurgeon in charge of the randomization process was asked to take the subsequent number on the list when completing the sick certificate of a patient ready for discharge. Patients were not aware of the other group's time to RTW. The sick certificate intended to make a clear recommendation of days additional to the injury day until RTW or individual usual ADL, while it did not give further instructions on how to behave during the recommended days until RTW. Beside the study, usual recommendations on when to RTW was made by means of a doctor's certificate issued at the discretion of the neurosurgeon on call. As part of the standard care of our hospital, an information sheet on mTBI was handed out to all mTBI patients, irrespective

of the study group allocation, including information on common symptoms associated with mTBI, instructions on how to gradually return to everyday ADL as well as symptoms and signs, which call for a follow-up (FUP) with a medical doctor. The outcome was determined in three outpatient FUPs within one week (T1), at three (T2) and twelve months (T3) post-injury. All patients were asked when they effectively returned to work, the workload (in %) and the time until they reached their pre-injury workload eight and fourteen days post-injury by phone as well as during the neuropsychological FUPs. Of note, the term "RTW" was also used for students and homemakers, describing the time until the patients returned to their pre-injury occupation. A detailed neuropsychological assessment was performed using a battery of validated neuropsychological tests in German language as described in Table 1 (see page 30). As a specific measure of PCS, patients rated the severity of 22 concussion symptoms for the preceding 24 hours on a 7-point Likert scale as part of the ImPACT, computing the Post Concussion Symptom Score (PCSS) (Maroon et al., 2000). Additional to comparing raw data, validated normative data stratified for age were used to determine T-scores, and to calculate composite indices of neuropsychological domains (Table 1). Health-related quality of life (HRQoL) was measured using the Short-Form (SF) 36 health survey. The recruited patients did not receive any other intervention to facilitate rehabilitation as part of the study other than mentioned above.

The primary endpoint was the difference in the PCSS three months post-injury (T2) between the study groups. Secondary endpoints were the difference in neuropsychological test performance including domain-specific and overall performance, RTW, the rate of ICD-10 criteria for PCS (three or more reported symptoms out of seven core symptoms: headache, dizziness, trouble falling asleep, fatigue, difficulty concentrating, difficulty remembering and irritability) at T1 to T3, as well as the difference in PCSS at T1 and T3.

Statistical analyses

Statistical analyses were performed using SPSS 22.0. Group comparisons were analyzed with unpaired, two-tailed student t-tests or Mann-Whitney-U tests. Pearson's chi-squared test (X^2) and the Fisher's exact test were used to evaluate the relationship between two categorical variables. P values < 0.05 were considered statistically significant.

2.5.3. Results

During the inclusion period a total of n=132 patients presented at the emergency department of the Cantonal Hospital St.Gallen with mTBI. N=102 patients were excluded from study participation due to inclusion or exclusion criteria or refusal to participate. The study had to be terminated in December 2013 due to logistic reasons. At this time point, 30 mTBI patients with a mean age of 35.0 years (18 to 55 years, 16 males and 14 females) were recruited. A complete neuropsychological assessment could be performed with n=27 patients at T1, n=24 at T2 and n=20 at T3. The reason for dropout in all cases was loss of motivation for further participation. One patient failed in the symptom validity test, screening for bad effort or malingering, and was thus excluded from further analysis. The occupational situation of the final study cohort of n=26 patients was: n=22 employed, n=3 students and n=1 homemaker Baseline characteristics are depicted in Table 11. The only significant difference was found in vocational class after primary education.

Table 11. Demographics of patients with mild traumatic brain injury (mTBI), as randomized in a group with either 3-day or 7-day sick leave post-injury

Parameter	*Study groups*		p-value
	3D-group	**7D-group**	
Age (years), M (SD)	32.46 (11.99)	40.00 (14.63)	0.164
Gender			**0.050**
Male	4 (30.8%)	9 (69.2%)	
Female	9 (69.2%)	4 (30.8%)	
Education (years), M (SD)	12.81 (1.97)	12.31 (3.13)	0.630
Vocational class[1]			**0.039**
1 – 3	4 (30.8%)	2 (15.4%)	
4 – 6	8 (61.5%)	4 (30.8%)	
7 – 9	1 (7.7%)	7 (53.8%)	
GCS at inclusion			0.372
15	11 (84.6%)	9 (69.2%)	
14	2 (15.4%)	4 (30.8%)	
Total	**n=13 (100%)**	**n=13 (100%)**	

Note. [1] Based on the International Standard Classification of Occupations (ISCO-88). *M*= Mean. *SD* = Standard deviation. GCS= Glasgow Coma Score.

A pathological overall result compared to normative data (T-score < 40) in the cognitive test battery was evident in three of 26 patients (11.5%) within one week, one of 23 patients (4.3%) at three months and none of the 19 patients at twelve months post-injury. The mean delay until RTW was 11.4 days, thus distinctly above both recommended sick leaves (Range 1 to 90 days). Table 12 shows the effective RTW time points. Notably only one patient of the whole sample (4.3%) complied with the assigned sick certificate. There was a trend for longer sick leave in patients randomized into the 3D-group (13.83±24.33 versus (vs.) 8.64±6.87, p=0.502). Due to the lack of adherence to the sick certificate by the vast majority of both groups we were only able to evaluate whether the instruction to rest alters the outcome not whether increased rest changes the outcome.

Table 12. Actual return-to-work in patients randomized to return-to-work after 3 days (3D-group) or 7 days of sick leave (7D-group)

	Before recommendation	According to recommendation	After recommendation
3D-group	2 (8.7 %) M: 1.5, SD: 0.71 Range: 1 to 2 days	0	10 (43.5 %) M: 16.30, SD: 26.13 Range: 4 to 90 days
7D-group	5 (21.7 %) M: 4.00, SD: 0.71 Range: 3 to 5 days	1 (4.3 %)	5 (21.7 %) M: 13.60, SD: 7.70 Range: 8 to 27 days
N=23 (100%)	7 (30.4 %)	1 (4.3 %)	15 (65.2 %)

Note. M = Mean of days going back to work. SD = Standard deviation.

Analysis of the primary endpoint

The group comparison did not show a significant difference in the total PCSS score between the D3-group and D7-group at three months post-injury (15.00±16.07 vs. 9.42±10.71, p=0.334).

Analysis of the secondary endpoints - One week post-injury (T1)

The study groups did not differ significantly in the total PCSS score (27.62±18.43 vs. 25.17±18.53, p=0.744). Analysis of subscores of the PCSS revealed significantly higher values in the symptom "nausea" for the D3-group (1.92±2.06 vs. 0.33±0.89, p=0.019). There were no group differences in any of the other symptoms at T1. From the 3D-group, 84.6% (11 out of 13) met the ICD-10 criteria for PCS compared to 66.7% (8 out of 12) in the 7D-group (p=0.378).

The results in the neuropsychological test battery showed significant group differences in four tests measuring two kinds of attentional functions, mental flexibility and visual memory (Table 13). The 3D-group showed better performance in the tests measuring divided attention, mental flexibility and visual memory, but more fluctuations in the selective attention test.

Table 13. Results from the neuropsychological test battery with significant group differences at T1 within one week post-injury

Measured cognition (unit) – test name	**3D-group** *M (SD)*	**7D-group** *M (SD)*	*t*	*p*
Divided attention visual cue (number of omissions) - TAP	0.50 (0.67)	1.69 (1.89)	-2,13	**0.049**
Selective sustained attention (fluctuations) - *Deux Barrage*	14.92 (6.53)	9.77 (3.03)	2.56	**0.017**
Mental flexibility (time of completion in s) - *TMT B*	52.17 (14.25)	78.46 (31.72)	-2,63	**0.015**
Visual retention late recall (number of points achieved) - VVM	11.23 (5.50)	7.08 (5.11)	2.14	**0.042**

Note. Lower values indicate better performance on the following tests: divided attention, selective sustained attention, mental flexibility. Higher values indicate better performance on the following test: Visual and verbal retentiveness. RT= reaction time. TAP= Test of Attentional Performance. TMT= Trail Making Test. MNND= Materials and Norm values for the Neuropsychological Diagnostics. M= Mean. SD = Standard deviation.

There were no group differences in any of the other cognitive tests, the domain-specific composite indices, the total composite index, the SF-36, the severity of symptoms regarding depression or anxiety nor for an adjustment disorder. The 3D-group showed higher values in three of twenty subtests of the stress inventory (Table 14).

Table 14. Significant group differences in stress regulation strategies measured with SVF-120 at the time point T2 (three months post-injury)

Factors	**3D-group** *M (SD)*	**7D-group** *M (SD)*	*t*	*p*
Mental preoccupation / rumination	17.80 (5.07)	12.18 (5.78)	2.36	**0.029**
Resignation	10.00 (5.21)	4.91 (3.78)	2.58	**0.018**
Aggression	9.90 (4.04)	5.09 (4.44)	2.59	**0.018**
Negative strategies	11.67 (4.15)	7.75 (3.87)	2.13	**0.048**

Note. M= Mean. SD = Standard deviation.

Three months post-injury (T2)

The 3D-group indicated significantly higher values of headache (2.55±2.38 vs. 0.17±0.58, p=0.005), while no difference was found in any other PCSS symptoms. Figure 1 illustrates the group-scores for each of the items of the PCSS. From the 3D-group, 45.5% (5 out of 11) met the ICD-10 criteria for PCS compared to 33.3% (4 out of 12) in the 7D-group (p=0.680). The 3D-group showed a faster or more accurate performance in four subtests that measure attentional functions and executive functions as well as in one composite score of the ImPACT (Table 15). In the SF-36 domain vitality, the 7D-group reached significantly higher values (16.92±3.59 vs. 13.18±4.22; p=0.028). There were no group differences in any of the other cognitive tests, the composite indices, the total composite index, or measures of depression, anxiety or adjustment disorder.

Table 15. Results from the neuropsychological test battery with significant group differences at T2 three months post-injury

Measured cognition (unit) – test name	**3D-group** *M (SD)*	**7D-group** *M (SD)*	*t*	*p*
Processing speed (time of completion in s) - *TMT A*	19.18 (7.11)	26.58 (7.80)	-2,37	**0.027**
*S*elective attention (omissions/min) - *Deux Barrage*	0.85 (1.03)	2.28 (1.62)	-2,51	**0.020**
Design fluency (total correct items) – *Design Fluency of MNND*	41.73 (8.59)	33.50 (7.88)	2.40	**0.026**
Mental flexibility (time of completion in s) - *TMT B*	49.09 (21.84)	71.50 (25.09)	-2,28	**0.034**
Visual motor speed composite - ImPACT	36.25 (12.32)	25.32 (9.71)	2.38	**0.027**

Note. Lower values indicate better performance on the following tests: *TMT A, Deux Barrage*, TMT B. Higher values indicate better performance on the following tests: *Design Fluency of MNND*, ImPACT. RT= reaction time. TAP= Test of Attentional Performance. TMT= Trail Making Test. MNND= Materials and Norm values for the Neuropsychological Diagnostics. M= Mean. SD = Standard deviation.

Twelve months post-injury (T3)

The 3D-group tended to show a higher mean PCSS score, but this group difference did not reach statistical significance (10.78±11.12 vs. 4.90±5.51, p=0.156). Twelve months post-injury, the 3D-group reported higher values in the items fatigue (1.89±1.76 vs. 0.30±0.95, p=0.043), sleeping less than usual (2.00±2.06 vs. 0.00±0.00, p=0.043) and nervousness (1.44±1.50 vs. 0.00±0.00, p=0.043). Four out of nine patients from the D3-group (44.4%) and one out of 10

patients in the 7D-group (10%) fulfilled the diagnostic criteria for PCS (p=0.141). Patients from the 3D-group reached a significantly better result in the visual motor speed composite of the ImPACT (39.43±8.19 vs. 31.25±5.44, p=0.028). The groups did not differ significantly in any of the other assessed cognitive measures, the composite indices, the total composite index, including also the tests screening for a depression, anxiety or adjustment disorder as well as the SF-36.

As treated analysis: Effective time to RTW

For the analysis of effective time to RTW, 23 patients were evaluated. A frequency analysis showed that 52.2% of the group returned back to work within seven days. The assigned workload at RTW varied between 25 and 100%. The days until patients reached their pre-injury workload varied between one and over 365 days. Two patients did not return to their previous workload. Due to the lack of adherence to the recommended days of rest by the majority of study patients, an "as treated analysis" has been performed splitting the complete patient cohort by the median; thus into a group that returned to work within seven days (≤D7-group) and a group returning to work after seven days (>D7-group). The two groups did not differ significantly in age, years of education, GCS status at inclusion, sex, vocational class or education (Table 16).

Table 16. Demographics of patients with mTBI, according to the "as treated" group assignment into a group that returned to work within seven days (≤ 7D-group) and a group that returned to work after seven days post-injury (>7D-group)

Parameter	*As treated groups*		p-value
	≤ 7D-group	**>7D-group**	
Age (years), M (SD)	38.33 (15.52)	38.00 (11.15)	0.953
Gender			0.220
Male	8 (66.7%)	4 (36.4%)	
Female	4 (33.3%)	7 (63.6%)	
Education (years), M (SD)	12.58 (1.99)	13.50 (3.01)	0.394
Vocational class[1]			0.340
1 – 3	3 (25%)	3 (27.3%)	
4 – 6	5 (41.7%)	5 (45.5%)	
7 – 9	4 (33.3%)	3 (27.3%)	
GCS at inclusion			0.559
15	10	8	
14	2	3	
Time to return-to-work (days), M (SD)	4.25 (1.82)	19.09 (24.16)	0.069
Total	**n=12 (100%)**	**n=11 (100%)**	

Note. [1] Based on the International Standard Classification of Occupations (ISCO-88). M= Mean. SD = Standard deviation. GCS= Glasgow Coma Score.

One week post-injury (T1)

There were no significant group differences regarding total PCSS scores between either groups (21.25±15.31 vs. 29.30±13.05, p=0.259) or any of the PCS symptoms. Ninety per cent (9 out of 10) of patients in the >D7-group fulfilled the criteria for PCS compared to 66.7% (8 out of 12) in the ≤D7-group (p=0.323). There were no significant group differences between the ≤D7-group and the >D7-group in the neuropsychological test battery.

Three months post-injury (T2)

At T2, patients of the >D7-group showed a strong tendency to be more affected by symptoms measured with the PCSS score (16.33±16.77 vs. 7.00±6.77, p=0.074). They showed significantly greater symptom severity in fatigue than patients of the ≤D7-group (2.60±2.32 vs. 0.58±1.08, p=0.029). Patients of the >D7-group were twice as likely as patients of the ≤D7-group to fulfil the PCS criteria according to ICD-10 (54.5% vs. 25.0%, p=0.214). There were no significant group differences in all other cognitive tests and questionnaires.

Twelve months post-injury (T3)

At T3, patients of the >D7-group still showed a tendency to be more affected by PCSS symptoms (10.78±11.48 vs. 4.90±4.82, p=0.156). The group returning to work after seven days showed again significantly higher symptom values in fatigue (13.30±133.00 vs. 0.10±0.32, p=0.017). At T3, criteria for PCS were still fulfilled by 55.6% (5 out of 9) of the patients of the >D7-group compared to none of the patients in the ≤D7-group (p=0.011). Most of the neuropsychological assessment was similar, except for worse performance of patients of the >D7-group on the fine motor speed task in the Grooved Pegboard (62.22±8.39 vs. 53.70±4.40, p=0.012). There were no significant group differences in all other cognitive tests and questionnaires.

2.5.4. Discussion

This was a prospective randomized parallel-group trial investigating the influence of an early (3D) vs. intermediate (7D) recommendation to RTW after mTBI on more favourable neuropsychological recovery. The study groups did not differ significantly in terms of the PCSS three months post-injury. Therefore, no significant recommendation can be made for appropriate standardization of sick leave certificates. Limitations of our study include a small sample size due to which statistical power is limited and results can only be seen as tendencies. The chosen analytics did not appropriately include the longitudinal design. Despite

randomization, there was an imbalance of vocational classes. The trial design had not anticipated a large lack of adherence of mTBI patients to the assigned RTW. The inclusion phase had to be terminated due to logistic reasons before achieving the necessary sample size.

At FUP time-point, there were no differences in the overall PCSS score between the two study groups. While the score was literally equal within the first week, tendencies for higher scores in the 3D-group at T2 and T3 post-injury became apparent. Higher symptom severity of nausea within one week post-injury could have a direct association to the assigned recommendation to RTW or ADLs after only three days of rest (Giza & Hovda, 2001, 2014; Iverson, 2005; McCrea et al., 2003; Silverberg & Iverson, 2013). The observed group differences in the stress inventory suggest that patients in the 3D-group were more likely to pursue negative strategies (including mental preoccupation or rumination, resignation and aggression) to regulate stress than patients in the 7D-group. Negative coping strategies are potentially capable of further enforcing the negative development of symptoms post-injury and might explain the higher symptom severity in nausea (at T1), headache (at T2) and fatigue, as well as less sleep than usual and nervousness (at T3) in the 3D-group compared to the 7D-group. This is in line with previous findings that highly symptomatic patients with acquired brain injury primarily use negative coping strategies (Velikonja, Warriner, Coulson, & Brum, 2013). The question remains if the group difference in vocational class could have influenced the use of stress regulation strategies between the groups. Our results suggest that more skilled workers tend to negative stress regulation strategies.

Patients of the 3D-group showed surprisingly better results in the vast majority of test scores that were different between the study groups. This would support the recommendation of a return back to pre-injury activities as soon as tolerated in recently published clinical practice guidelines.(Marshall et al., 2015) Again, the higher mean vocational class of the 3D-group can play a role, as training in more skilled work usually leads to better results in cognitive test performance. Interestingly, however, no group differences in the duration of education or in the intelligence test were found, which are also prone to influence cognitive test performance. The sub-score fluctuations in the “Deux Barrage” test measuring selective and continuous attention at T1 was the only sub-score of the cognitive test battery, where the 7D-group reached a better result. This result represents more fluctuation during a 10-minute task, which can be a sign of fatigue, possibly due to higher symptom severity in patients with a short recommendation to RTW.

Despite a physician's recommendation, nearly half of the patients did not feel ready to return to their pre-injury occupation at one week post-injury. A systematic review of RTW after mTBI summarized that most people are returning to work within three to six months after mTBI (Cancelliere et al., 2014). Both the median (7 days) and mean time until RTW (11.4 days) were considerably shorter in our sample than in the sample of Losoi et al., which had a median of 16 days and mean time of 26.1 (sub-sample with no PCS at twelve months) or 146.4 days to RTW (sub-sample with mild PCS at twelve months) (Losoi et al., 2015). We believe that the mere recommendation of two certain times until RTW by means of a sick certificate did influence the duration until RTW positively, since it suggested to the patients that a rapid recovery from mTBI can be expected and RTW after a week is generally anticipated by the doctors.

While further research is needed to identify predictors of delayed RTW, our data indicate that patients with a real sick leave of more than seven days have a less favourable mid- and long-term prognosis. Our analysis showed without doubt two patterns of patients that differ greatly: early RTW with full workload and less PCS symptoms and later RTW with less workload and more PCS symptoms. Here, our results resemble the findings described in the literature (Majerske et al., 2008; Marshall et al., 2015). In our study cohort, the overall cognitive test performance was below the cut-off compared to normative data (T-score < 40) in three patients at T1, in one patient at T2 and in none of the patients at T3, which is in accordance with the current literature (Karr, Areshenkoff, & Garcia-Barrera, 2014). Interestingly, the subject with a pathological finding at T2 was one of the two patients who returned to work even before three recommended days. The two patients, who were not back to their previous workload at T3 did, however, not show impaired results (T-score < 40). These observations suggest a relative independence of RTW issues from cognitive test performance.

The results of the "as-treated analysis" suggest that a RTW within one week post-injury is more beneficial than a RTW after one week, but we cannot prove a causal relationship. The results from the "intention-to-treat analysis" indicate that an initial intermediate recommendation to RTW of seven days is more beneficial than a short recommendation of three days. With simultaneous consideration of both results, considering recent recommendations and taking our clinical experience into account, we recommend an initial recommendation to RTW of four to seven days, when an mTBI patient seeks doctor's advice immediately after injury. Patients should be reassured that a good recovery from mTBI can generally be anticipated. If gradual RTW fails within three weeks post-injury, a physical or cognitive performance test should be

performed, involving the skills of his pre-injury job as much as possible to objectify occurring symptoms and impairments. Following this, counselling by a psychologist, occupational therapist, physiotherapist or medical doctor is advised to educate and support him in the dealing with the persistent symptoms and possible cognitive and/or physical impairments taking the work environment into account and to accompany her/him in the gradual RTW.

Conclusions

There was no significant difference in the intention-to-treat analysis of the PCSS three months post-injury between patients randomized to resume work after three or seven days of sick leave. In the as-treated analysis, patients that returned to work within seven days post-injury resumed with a higher workload, showed less fatigue, less clinical signs of PCS as diagnosed according to ICD-10 criteria, and showed no neuropsychological impairment in the short-, mid- and long-term interval. Our data support the heterogeneity of mTBI and shows that acute and sub-acute symptoms are not prognostic factors for neuropsychological outcome at one year.

3. GENERAL DISCUSSION

In the following chapter the findings from the three sub-studies are integrated in an overall discussion by relating them to the four presented research questions and general conclusions as well as clinical implications are drawn. Finally, consequences and ideas for future studies are discussed. The main focus of the general discussion is on evaluating the contribution of this PhD thesis to the management of mTBI patients in regard to diagnostic imaging methods for prediction of pPCS / unfavourable cognitive outcome and on recommendations for return to work.

3.1. Integration of findings

The first aim of this PhD thesis was to increase the knowledge about diagnostic techniques acquired on a MRI-scanner in the prediction of pPCS and unfavourable cognitive outcome and to learn more about the pathophysiology of mTBI over the period of one year. The following paragraphs focus on answering the two research questions focused on this aim.

Answers to research question 1:

Which MRI-techniques are able to predict pPCS and unfavourable cognitive outcome in patients with mTBI?

With the literature review summarized in the first publication, we could partially answer the first research question. Partially because we did not find studies evaluating the selected MRI sequences as predictors of unfavourable cognitive outcome, but only in regard to pPCS. Additionally, the answer is not comprehensive since we did not evaluate all MRI sequences which have been studied in the context of mTBI (Eierud et al., 2014). The conclusion of our literature review was that DTI, SWI, MRS and resting-state fMRI have adequate sensitivity and specificity as predictive diagnostic tools for pPCS (Studerus-Germann et al., 2016). Based on this conclusion we chose two of the evaluated MRI sequences for this PhD-project: SWI and DTI. SWI was chosen since it was already starting to be in clinical use in our hospital and beyond in patients with mTBI due to its sensitivity to mTBI-related cerebral MB (Sharp & Ham, 2011). DTI was chosen since its sensitivity to microstructural changes in white matter integrity in mTBI-patients had been implicated (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008). An additional motivation to choose DTI was that many of the previous studies involving DTI as diagnostic tool in mTBI emphasise the need for longitudinal studies in combination with neuropsychological assessments to evaluate its possible use as prognostication tool and to improve the assessment of the time course of DTI changes. We

decided against the use of MRS and fMRI, primarily because of missing experience with these methods in our hospital. For fMRI the practicability in daily clinical practice had been questioned before in our hospital, especially due to limited infrastructure and human resources.

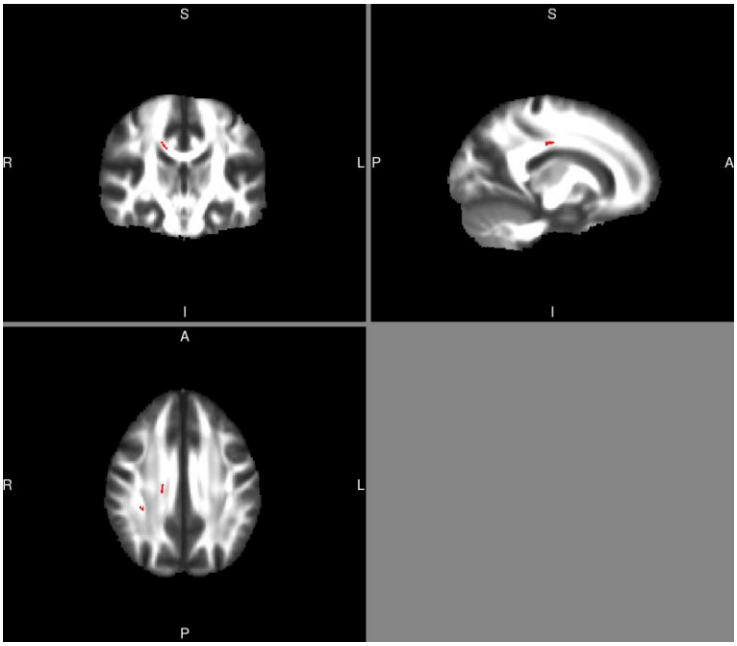
The results of our empirical study showed that mTBI patients with MRI findings possibly associable with the TBI in the acute state, including MB, contusion, haematoma or oedema, had higher symptom values in cognitive symptoms such as slowing, difficulty in memory and concentration than mTBI patients without MRI findings, but no differences in effective cognitive performance in a comprehensive battery of validated neuropsychological measures. This indicates that pathological MRI findings can possibly predict higher cognitive symptom values, but not cognitive performance. Meanwhile mTBI patients with MB showed worse performance in several cognitive tests over all three times of follow-up and higher symptom severity in PCSS after twelve months. More MB were correlated with worse cognitive performance at all three times of follow-up and higher symptom severity at one year post-injury. Therefore we concluded that SWI is able to detect MB, which can be considered as prognostic factors for pPCS and cognitive outcome in mTBI patients (Studerus-Germann et al., 2016) in accordance with findings from Huang et al. (2015). In accordance with our findings for mTBI patients, a recent study evaluating cerebral MB in hemodialysis patients concluded that MB were a risk factor for cognitive dysfunction and additionally they found a correlation between the location of MB and cognitive impairment (Chai et al., 2016). A recent review on cerebral MB in general, not specifically focusing on MB caused by mTBI, reasons that white matter deterioration is the possible explanation why MB cause cognitive impairment (Wu & Chen, 2016). Ultimately SWI would be an answer to the first research question.

In the acute phase within a week post-injury we did not find any statistically significant differences in DTI measures between our sample of mTBI patients and our control group. Due to those missing differences, we could not analyse correlations between differing DTI measures and pPCS or cognitive outcome.

When grouping the mTBI patients according to PCS status, based on symptom reporting at three months post-injury, small differences in FA in the right hemisphere were found in mTBI patients with PCS compared to controls (see Figure 4) by means of TBSS-analysis, while no differences were found in mTBI patients without PCS versus controls. A difference in DTI-measures between PCS positive mTBI patients according to ICD-10 criteria evaluated six to

eight weeks post-injury compared to a control group and no difference between PCS negative mTBI patients compared to a control group was also found in a recent study (Lange et al., 2015). In contrast to our study they only scanned their mTBI patients in the sub-acute phase 6-8 weeks post-injury and they found significant differences in MD and RD and only a trend ($p < 0.10$) in FA in the PCS positive group compared to controls with lower values in the PCS positive group. Another study, which evaluated their mTBI patients seven to 28 days post-injury with DTI and grouped them according to their PCS-status at three to four months post-injury, reported differences in MD, between PCS positive mTBI-patients and controls, but in contrast to the findings from Lange et al their PCS positive group showed higher MD values than controls (Messe et al., 2011).

These findings implicate an association between PCS-status and DTI-measures. Nevertheless, DTI was not able to predict pPCS in our study when looking at the whole group of mTBI patients and when comparing patients according to PCS-status to controls their differences in DTI-measures vary in regard of the specific DTI-measures and directions, therefor DTI seems not yet ready to serve as a predictive tool for pPCS or cognitive outcome in clinical practice.



The red areas highlight regions where FA in controls was lower than in PCS positive mTBI patients in our sample.

Note. PCS = Post Concussion Syndrome, TBSS = Tract-based spatial statistics, FA = fractional anisotropy.

Figure 4. Significant group differences between controls and PCS positive mTBI patients of TBSS analysis of FA maps within one week post-injury

Answers to research question 2:

What can we learn about the pathophysiology of mTBI over the period of one year by means of MRI and specifically SWI and DTI?

In the acute phase one third of our mTBI group (10 out of 30) showed at least one pathological finding associated with the TBI by means of MRI, such as MB, contusion, haematoma or oedema, while two thirds (20 out of 30) did not show a MRI finding associated with the mTBI. Since no pathological finding was detected in any of the patients by means of the initial CT scan, this gives further proof that MRI is more sensitive to pathologies caused by mTBI than CT in accordance with Paterakis et al. (2000). SWI was able to detect MB in four out of our sample of 30 mTBI patients in the acute phase. In contrast to this result, a recent study evaluating ice hockey players at the beginning of the season and after suffering a mTBI concluded that mTBI does not lead to new MB (Jarrett et al., 2016). In the MRI-scan one year post-injury, MB were the only remaining MRI finding possibly associable to the mTBI in our sample. This indicates that the brain recovers from the other pathologies found by means of MRI within a year. Of the four mTBI patients which had shown MB in the acute phase, two showed up for follow-up after one year and they persistently showed MB. A recent study with military service members who had suffered a TBI showed that the number of MB and quantitative susceptibility maps decreased over time in their sub-sample of 13 patients, which had MB at baseline MRI (885 +- 1161 days post-injury) and where followed-up 270 ±144 days later (Liu et al., 2016). Their long time between baseline and follow-up and their heterogeneity of the group (3 of the 13 followed-up patients where mTBI, while the other 10 were more severe TBI) make a comparison to our data difficult. Their study pointed out that a more detailed analysis of the number and size of MB, plus the quantitative susceptibility maps between baseline in the acute phase and after one year would be interesting to learn more about the longitudinal development of MB.

To our surprise two mTBI patients showed MB in the follow-up one year post-injury, which had not shown MB in the acute phase. One of the two had reported that he had suffered a second mTBI four months after the initial mTBI and his new MB was lead back to this second impact, in line with the assumption that mTBI can cause MB. The cause of the MB of the second patient showing them at follow-up only, was not known.

Interestingly, by means of SWI haemosiderin deposits were detected in both evaluated groups – the mTBI patients and the control group in our study, which questions its cause. The

haemosiderin deposits in the six mTBI patients in the acute phase were associated with the mTBI, which was supported by the fact that all expect one of those patients showed additional MRI findings such as contusion, haematoma or oedema, most probably caused by mTBI. MRI-data from before injury would be needed to decide if the MB in the mTBI patients were definitely caused by the injury. In the five out of 19 healthy controls, in which haemosiderin deposits were found, the neuroradiologist associated two with calcification, one with microangiopathy and two were labelled as possible MB, possibly due to unknown degenerative disease. Further research is needed to evaluate MB by means of SWI to learn what they can tell us about their cause and if the detection of MB is a sensitive measure for prognosis.

In the present study, correlations between higher numbers of MB and higher values in the DTI parameters MD, AD and RD were found, which could be explained by the structural damage to the tissue induced by the MB, which leads to weaker constraining of water molecule movements, more freely moving water and therefore higher values of MD, AD and RD.

As mentioned before, the comparison of DTI-measures between our sample of mTBI patients in the acute phase within a week post-injury and the healthy control group did not reveal any significant differences between groups. This indicates that there were no significant pathologies detectable with DTI in the acute phase in our patient sample as a whole. No comparison between individual patients and the mean of healthy controls was performed, therefore we cannot tell if some of the individual patients showed pathologies. Few studies have used analysis techniques in DTI data to detect inter-individual differences as would be needed for clinical practice. Receiver Operating Characteristic (ROC) analyses showed EZ-MAP (specificity 71%, sensitivity 71%) to be able to discriminate mTBI patients from controls in terms of the total number of abnormal white matter voxels detected in a study focusing on the analysis of individual mTBI patients (Kim, Branch, Kim, & Lipton, 2013).

In contrast to missing significant results for the whole sample of mTBI patients compared to controls, the grouping of patients according to PCS status showed that DTI is able to detect pathophysiological processes in the acute phase post-injury if mTBI patients with psychopathological symptoms were selected from the sample. This reinforces the assumption that persistent symptoms are linked to pathophysiological processes and confirms the importance of classifying mTBI patients according to severity of symptoms, respectively PCS

status as stated by several authors (Dall'Acqua et al., 2016; Messe et al., 2011; Waljas et al., 2014).

When comparing the DTI-measures from the mTBI patients from one year post-injury to the control group, significant differences were found in nearly all image type in widespread regions, which possibly reflects axonal degeneration. This indicates that DTI measurements in the late phase post-injury could possibly be used as proof of occurred mTBI in comparison to healthy controls and that DTI could be a valuable tool to evaluate posttraumatic processes in the later phase post-injury.

Our comparison of DTI-measures between the mTBI patients in the acute and the late phase post-injury showed significant differences, with higher values in the acute phase. The group differences can possibly be accounted to the pathophysiological recovery process taking place over the period of one year following a mTBI. Though some of the differences might even occur in healthy individuals over the period of one year and are therefore not pathological.

The second aim of this PhD thesis was to evaluate the influence of two recommended specific times respectively the effective time until return to work or school on the development of PCS and cognitive outcome over a period of one year with follow-ups in the acute (within seven days), the semi-acute (after three months) and the late phase post-injury (after twelve months) (see paper 3 for results). The following two paragraphs focus on answering the two research questions focused on this aim.

Answers to research question 3:

Is a short or intermediate time to return to work after mild traumatic brain injury more favourable with regard to pPCS and cognitive outcome?

We assume that a period of strict mental and physical rest combined with temporary analgesic medication enables the cascade of neurochemical changes after mTBI to normalise. To find out how two specific durations of rest influence outcome we randomly allocated our sample of mTBI patients into a group with a short period of rest of three days (3D-group) and a group with an intermediate period of rest of seven days (7D-group) as recommended with a doctor's certificate at the time of presentation at the emergency department. We expected the majority of patients to obey to the doctor's certificate, especially since it was explicitly stated as one of the purposes of the current study in the informed consent form. To our surprise the analysis of

effective time until return to work showed that only one patient of the whole sample had complied with the instructions of the sick certificate. The group receiving a doctor's certificate for three days effectively returned to work later than the group, which had received a doctor's certificate for seven days. The mean delay until return to work was with 11.4 days distinctly above both recommended sick leaves. The results from the "intention-to-treat analysis" indicated that the group with an initial short recommendation to return to work of three days tended more to negative strategies (maladaptive strategies including mental preoccupation or rumination, resignation and aggression) to regulate stress according to the stress inventory SVF-120 and they showed worse outcome in regard of specific post-concussion symptoms (nausea at T1, headache at T2 and fatigue, less sleep than usual and nervousness at T3) and PCS than the group with an initial intermediate recommendation to return to work. At three months post-injury the 7D-group reached higher values in the domain vitality of the health survey SF-36, indicating a greater sense of vitality, than the 3D-group. It remains unclear if the two groups already differed in regard of the maladaptive strategies before trauma and it therefore acted as a confounding factor or if it was a result of the recommended duration of sick leave. However, negative coping strategies are potentially capable of further enforcing the negative development of symptoms post-injury and might explain the higher symptom severity, lower sense of vitality in the 3D-group compared to the 7D-group.
Meanwhile the 3D-group showed a better cognitive outcome in the vast majority of test scores, which were different compared to the 7D-group. A possible confounding factor for the better performance of the 3D-group was that despite randomization, they showed a higher level of mean vocational class after primary education than the 7D-group and training in more skilled work usually leads to better results in cognitive test performance.

A literature search looking for recent empirical studies on recommended return to work in mTBI-patients has not provided new information. Summarizing from the "intention-to-treat analysis", the recommended duration of time until return to work influenced the post-concussion symptoms and cognitive outcome in opposite directions. Therefore, the answer to the third research question based on our results is that an intermediate recommendation to return to work seems more favourable in regard to post-concussion symptoms while a short recommendation to return to work is possibly more favourable for neuropsychological test performance. Recently a study found being sick-listed at two months post-injury amongst other variables to be predictive for return to work at one year (Vikane et al., 2016), which can be

interpreted that the sick status itself is a possible predictor of prolonged sick status. Therefore, the duration of sick leave should be chosen carefully.

Answers to research question 4:

How does the effective time until return to work influence pPCS and cognitive outcome?

The effective time until return to work was enquired from the patients by phone eight and fourteen days post-injury by the study nurse and at neuropsychological follow-ups and its influence on post-concussion symptoms and cognitive outcome three and twelve months post-injury was analysed. Despite the recommendation of the doctor's certificate, nearly half of the patients of our sample did not feel ready to return to work at one week post-injury. However, the median (7 days) and mean time until return to work (11.4 days) was considerably shorter in our sample than in a recently published study (Losoi et al., 2015), which had shown a median of 16 days and mean time of 26.1 (sub-sample with no PCS at twelve months) or 146.4 days to return to work (sub-sample with mild PCS at twelve months). All of the patients of our sample had returned to work within three months post-injury, which is on the bottom of the range of three to six months until when a systematic review of return to work after mTBI summarized most mTBI patients to have returned to work (Cancelliere et al., 2014).

The results of the "as treated analysis" indicate that patients with a real sick leave of more than seven days have a less favourable mid- and long-term prognosis than patients returning to work within a week. At follow-ups three and twelve months post-injury patients returning to work within a week showed less symptom severity in fatigue and they were less likely to fulfil the PCS criteria according to ICD-10 than the group returning to work more than a week post-injury. In regard of cognitive outcome, the only group difference was found twelve months post-injury in a fine motor speed task with the group returning to work more than a week post-injury showing slower task completion with the dominant hand than the group returning to work within a week. Those results from the analysis of effective time until return to work indicate that patients returning to work within a week show less post-concussion symptoms mid- and long-term and better cognitive outcome long-term compared to patients taking longer to return to work. Since the two groups did not show any difference in regard of symptom severity in the acute phase or in the vocational class at time of injury or any other possible confounding factor that we could think of, it remains unanswered why the patients of the one group took longer to return to work.

3.1.1. Limitations

There are some overall limitations of this project, some of which are at the same time of the most important lessons learned for me as PhD student. The first limitation which had great influence on the data collection, analysis and publication was the initial shortcoming to define a set amount of statistically verifiable hypotheses. This led to a vast amount of chosen measured values, a missing initial concept during data analysis and eventually missing structure in the publication of results. The lack to select a small amount of hypotheses probably arose due to the great enthusiasm of the study team to get as much clinical information as possible out of the project, the limited experience in the conception of experimental studies and the limited statistical knowledge of the study team. Consequently, the discussion of analytical techniques with statistical experts, not familiar with the neuroscientific field, did not result in a more structured analytical concept. To correct for alpha error accumulation due to multiple comparisons in small samples the Bonferroni correction should have been performed. Additionally, effect sizes for all comparisons should have been reported to rise the informative value of the results despite the small sample size.

In paper 2 and 3 it has already been discussed that the limited sample size was the biggest limiting factor when it comes to the validity of the data interpretation and the representativeness of the recruited sample for the whole population of mTBI patients. In the following, factors are discussed, which probably led to the limited sample size. In the first place the number and duration of follow-up visits (three follow-up visits with each approximately 2.5 hours for neuropsychological examinations and additional 0.5 hours for MRI at two of the three visits) put probably many patients off from participating in the study in the first place and led to drop-outs once patients did not suffer from the injury anymore. Looking at the conception of the study, the number of follow-ups still seems interesting with the chosen methods and actually many past studies with MRI had suggested future studies with a longitudinal design (Benson et al., 2007; Inglese et al., 2005; Miles et al., 2008; Niogi & Mukherjee, 2010; Wilde et al., 2009). The duration of the visits on the other side could have been reduced by limiting the selection of neuropsychological tests and psychological questionnaires. This at the same time would have reduced the vast amount of data, which was difficult to overlook during data storage and analysis, while still leading to simular conclusions. Looking back it would have even been a possibility to consider to leave away MRI scans, since focusing on return to work and pPCS would have probably also allowed interesting knowledge gain. This would have reduced the economic burden, logistic complexity and data amount of the study considerably.

Sticking to the chosen project conception the way to raise the number of recruited patients was by improving the motivation of the recruiters to motivate more patients to participate. From the beginning of the study, it was agreed that the neurosurgeon on call would receive a certain bonus for each recruited patient as a source of motivation, and this was communicated to the investigators during training. This idea came up in the first place, because most of the neurosurgeons were in general not highly motivated to spend much time on patients whom they cannot treat with their main vocation (surgery), which is normally the case with mTBI patients. To our surprise, the financial bonus did not motivate most of them. The recruiting was most probably further negatively influenced after the principal investigator amongst the neurosurgeons had to be changed from the initial founder of the study project, who was highly motivated for the project and would have therefore volunteered to recruit patients whenever possible or convinced his colleagues to do so, to some other neurosurgeon at will. This difficulty in recruitment also questions if mTBI patients could profit more in their initial treatment if they were handled by medical doctors from another speciality such as general practitioners, emergency department staff or neurologists. The option to recruit patients on the phone also arose, but would probably have led to a recruiting bias, since more patients with persistent symptoms would have agreed to participate.

In regard of the MRI-data the study team lost its initially assigned neuroradiologist after the parameters of the MRI-protocol and the documentation of diagnostic findings were completed. The MRI-scans were adjudged by one of several neuroradiologists on duty. During analysis of MRI-data and interpretation, supervision by an experienced neuroradiologist would have been helpful and would probably have allowed gaining more knowledge from SWI-data in regard of differences between mTBI and healthy controls in the regional distribution and appearance of the MB. A subsequent project has been discussed based on the MRI-data of this PhD-project to gain further knowledge.

3.2. Knowledge gain: Implications for clinical practice and future research

3.2.1. Implications for clinical practice

Diagnostic with MRI

The results from our literature review and our sub-study on MRI-sequences have confirmed that MRI is more sensitive to pathologies caused by a mTBI than CT and that MRI is able to detect pathologies possibly attributable to the mTBI such as MB, contusion, oedema and haematoma, which were associated with higher symptom values in cognitive symptoms such

as slowing, difficulty in memory and concentration. Additionally, SWI showed to be able to detect MB, which are potential prognostic factors for pPCS and cognitive outcome in mTBI patients. Therefore, a MRI-scan including SWI early after injury could help decide if further follow-ups are needed, especially since it is suitable for clinical practice and for evaluation of individual patients. But the question remains how much benefit we get from a SWI additional to the evaluation of risk factors for pPCS and delayed return to work.

Our comparison with DTI between mTBI patients in the acute and the late phase post-injury showed significant differences, which can be possibly accounted to the time course and implicates that the pathological processes increase over time. If this results can be replicated, this could indicate that DTI could be a valuable tool to evaluate posttraumatic processes in the later phase. Based on our experience DTI does not seem ready yet as a diagnostic tool for the clinical setting since its analysis is too time consuming and so fare little knowledge exists about the analysis of individual patients, which would be needed for clinical use.

Finally, time economic and logistic considerations speak against a regular use of MRI since MRI scans are expensive and the availability of scan time is limited due to the growing demand in most hospitals. Personally, I would rather spend the time and money on further follow-ups with the patient than for a MRI-scan. Probably newer MRI-techniques remain interesting for insurance reasons, if they allow a reliable discrimination between patients having suffered an mTBI and such which have not, since so far this discrimination relies merely on subjective evidence.

Return to work and follow-ups after the acute phase

The results from our sub-study on return to work indicated firstly that when patients present to the emergency department with a mTBI, an intermediate recommendation of seven days until return to work is more beneficial than a short recommendation of three days until return to work and secondly that return to work within one week post-injury is more beneficial than after one week, in regard of persistence of symptoms. With simultaneous consideration of both results and recent recommendations on return to work in mTBI guidelines (Marshall et al., 2015; New South Wales Motor Accident Authority, 2008), an initial recommendation of four to seven days of rest before patients return to work as prescribed with a doctor's certificate seems most beneficial, when a mTBI patient seeks doctor's advice immediately after injury and they can be discharges without further treatment. The involved medical staff of this PhD-study including

representatives from the emergency department, the neurosurgery and neuropsychology department would rather choose a duration of rest on the longer side of this range of four to seven days, to prevent the patients from initial stress, to test their mental and physical capacity and the occurrence of symptoms in an environment, where they are probably more flexible to switch between performance and breaks as needed. During the recommended period of rest the patient should try to resume his daily activities such as homework, light exercise such as walking and social contacts as soon as tolerable and build up the duration and intension of activities stepwise, taking breaks if symptoms increase. From our experience the need of sleep can be prolonged in the acute phase after mTBI and a study found 43% of uncomplicated mTBI patients reporting sleeping more than before injury at one week post-injury (Ponsford, Cameron, Fitzgerald, Grant, & Mikocka-Walus, 2011). Meanwhile patients should try to limit sleep to nightly sleep as soon as possible to prevent them from getting their normal sleep and activity rhythm mixed up and sleep hygiene counseling can support them in dealing with sleep disturbance. If a patient is free of symptoms before the recommended time of rest and if no safety reasons speak against it, he can already start with a gradual return to work. After seven days of relative rest the patient should return to work at least part-time and build up his job routine gradually. Based on our results and current literature we recommend that mTBI patients, who do not feel ready to return to work after seven days, should be followed-up with greater attention in weekly follow-ups with a medical doctor or neuropsychologist. To help decide about further treatment, factors that have shown to be predictive for return to work, respectively that increase the risk of persistent symptoms should be evaluated (Friedland & Dawson, 2001; Levin & Diaz-Arrastia, 2015; MTBI Guidelines Development Team, 2010; Stulemeijer et al., 2008; Vikane et al., 2016):

- history of previous TBI
- psychiatric or neurological problems before injury
- sick-status before injury
- duration of formal education (> 11 years being of advantage)
- independence and decision-making latitude of the job (greater latitude being of advantage)
- level of social support
- acute anxiety, depression, nausea or vomiting on hospital admission
- early onset of pain
- psychological distress (e.g. measured with the Hospital Anxiety and Depression Scale (HAD))
- global functioning (e.g. measured with the GOS).

Regular contact to the employer should be kept and possibilities for modified work, respectively gradual resumption of demands for initial return to work should be discussed. A recent review article suggested a letter to employers requesting gradual resumption of demands might mitigate secondary disorders and enhance recovery (Levin & Diaz-Arrastia, 2015). If gradual return to work fails within three weeks post-injury, a physical or cognitive performance test (depending on the type of job, by a neuropsychologist, occupational therapist or physiotherapist) should be performed, involving the skills of his pre-injury job as much as possible to objectify occurring symptoms and impairments. Following this, counseling by a psychologist, occupational therapist, physiotherapist, social worker or medical doctor is advised to educate and support him in the dealing with the persistent symptoms and possible cognitive and/or physical impairments taking his work environment into account (e.g. complexity of tasks, responsibility level, time pressure, environmental stressors like noise, heat and strain to the body) and to accompany him in the gradual return to work.

General implications for clinical management of mTBI

Regardless of the duration of sick leave, we recommend that all patients should be given brief verbal and written instructions in the emergency department before discharge in line with the recommendations in recent mTBI guidelines (Marshall et al., 2015). A recent systematic review about the effectiveness of early educational interventions in the emergency department to reduce incidence or severity of PCS following a mTBI has summarized that three of the five evaluated studies suggested that early educational or advice interventions reduced the frequency of either composite or individual PCS (Eliyahu, Kirkland, Campbell, Rowe, & Carpenter, 2016). A previous systematic review on psychological approaches to treatment of PCS concluded information, education and reassurance alone may not be as beneficial as previously thought, despite this they still suggest that brief information and explanation should be provided in the emergency department (Al Sayegh, Sandford, & Carson, 2010). Two of the reviewed studies, which were published several decades ago, showed that with information and reassurance respectively additional continuity of care, encouragement and physiotherapy, time off work could be reduced by one respectively two weeks compared to routine care (Hinkle, Alves, Rimell, & Jane, 1986; Relander, Troupp, & Af Bjorkesten, 1972). Al Sayegh et al. (2010) also concluded in their review that cognitive behavioural therapy showed some promise in the management of PCS. Both reviews conclude that evidence is not of sufficient quality to provide clear recommendations and that well designed studies are needed to gain more recommendations for the clinical management of mTBI patients.

Practical implications for the aftercare of mTBI-patients in the study hospital

On the base of gained knowledge in this PhD-project, a new concept for the aftercare of mTBI patients was developed for the Cantonal Hospital St.Gallen. It was decided to recommend mTBI patients suffering from symptoms during their first examination a follow-up visit one week later in the general practitioner walk-in clinic or emergency department. Alternatively, a medical doctor from those two departments contacts the patient one week post-injury over the phone. Main focus of this follow-up is to hear how the patient recovers, to evaluate if she/he suffers of persistent symptoms (by means of a standardized questionnaire developed based on the Rivermead Post Concussion Questionnaire (RPQ)), to discuss return to daily activities, especially return to work or extension of the doctor's certificate and to decide if a further follow-up visit is needed. If the patient feels well recovered and able to return to work one week post-injury, no further follow-up is planned. If patients suffer mainly from persistent somatic symptoms possible visits with other specialists, e.g. a neurologist in case of persistent headaches or dizziness, are considered. If patients suffer mainly from persistent affective and cognitive symptoms, a copy of the questionnaire with persistent symptoms is sent to the division of neuropsychology for them to contact the patient for an ambulant visit based on principles from cognitive behavioural therapy. Several studies showed that cognitive behavioural therapy in sessions of 50 to 60 minutes led to significant improvement compared to waiting list controls, and we hope this effect can be replicated with the new concept of aftercare in the Cantonal Hospital St.Gallen (Hodgson, McDonald, Tate, & Gertler, 2005; Mittenberg, Tremont, Zielinski, Fichera, & Rayls, 1996; Tiersky et al., 2005). The evaluation of this new concept for aftercare should be content of future research.

3.2.2. Implications for future research

Personally I hope future research puts more emphasis on the aftercare of mTBI patients rather than spending the main focus on modern diagnostic measures, such as MRI, as has been the case in the last decade. The main reason for this focus on diagnostic measures is most probably the hope that improved diagnostic allows a better selection of mTBI patients who should receive further follow-up. At the same time several short follow-ups by a medical doctor or neuropsychologist could be performed to reach the same amount of costs as a single MRI-scan and already a single follow-up would probably allow more individual selection of patients in need of continued treatment. Since return to work and occupational status are of the best indicators for everyday functioning (Ownsworth & McKenna, 2004), future research should use return to work as outcome measure additional to symptom persistence / PCS after mTBI. A

past study used a combination of PCS-status (as defined by ICD-10 criteria), work status and subjective judgement of activities and participation (measured with the Rivermead Head Injury Follow-Up Questionnaire (RHIFUQ)) and summarized from their experience that it appears useful and requires further validation (Snell, Siegert, Hay-Smith, & Surgenor, 2011).

Since all patients in the working age are in need of recommendations on when to return to work post-injury, we suggest future research on effective return to work and randomized trials, e.g. comparing our finding of a recommendation of seven days until return to work as prescribed with a doctor's certificate with previous handling.

Our study showed a difference in the strategies to cope with stress between the randomization groups, with the group tending to negative strategies (maladaptive strategies) showing worse outcome in regard of persistent symptoms. This finding aroused my interest for future studies on coping strategies in mTBI patients and their influence on return to work and persistence of symptoms. A brief literature search for corresponding studies revealed that mTBI patients that used avoidant coping showed worse emotional functioning and quality of live outcomes three months post-injury (Maestas et al., 2014). Contrary to this finding, a previous study showed that mTBI patients which used approach or active coping strategies when faced with stressful situations were associated with poor outcome at three months post-injury (Snell et al., 2011). Those two findings already implicate that future trials evaluating beneficial coping strategies and involving them in interventions that teach such coping styles could be of interest.

There are several treatment studies mainly from the last Century, which included the teaching of coping skills in their early interventions for mTBI patients, but it is difficult to replicate their interventions due to missing detail information on the taught coping skills (Gronwall, 1986; Hinkle et al., 1986; Minderhoud, Boelens, Huizenga, & Saan, 1980; Ponsford et al., 2002; Wade et al., 1998). A more recent pilot study offering a short intervention by a social worker in the emergency department, showed that the treatment group maintained pre-injury levels of community functioning, lower symptom scores, lower scores on the Patient Health Questionnaire (PHQ-4) and on the Post-traumatic Stress Disorder Checklist-Civilian (PCL-C) compared to the group receiving the usual care (Moore et al., 2014). Their intervention included suggestions for coping strategies, along with education on common symptoms, return to work / timelines for recovery, brief educational alcohol intervention, reassurance and education about recovery process / follow-up guidelines, community resource provision, discussion of patient

questions, take home packet of information and resources. But their publication did not include further information on the suggested coping strategies.

In general future studies should focus on the evaluation of treatments that are suitable for clinical practice such as short follow-ups by (neuro)psychologists, social workers or nurses. Previous studies reported fewer PCS symptoms and less stress three months post-injury, respectively lower symptom frequency and severity, and earlier resolution of symptoms in their treatment groups receiving a follow-up with a therapist within the week post-injury including specific written instructions (Mittenberg, 1996; Ponsford et al., 2002). A randomized trial showed that patients receiving five scheduled telephone calls over the first three months post-injury focusing on symptom management and encouraging an early return to everyday activities, were even less likely to experience post-concussion symptoms six months post-injury, to report altered ability to work, reduced function in leisure or recreational activities, in memory or concentration and reduced financial dependence, than their comparison group, which just received written information at the emergency department (Bell et al., 2008). Since they could not identify the specific elements, which led to the successful outcome, they recommend further similar studies.

Additional to studies involving information and reassurance in the aftercare of mTBI-patients, there is evidence that cognitive behavioural therapy, mindfulness training and other self-management techniques might be useful in the reduction of symptoms in mTBI patients in the sub-acute phase (Al Sayegh et al., 2010; Mittenberg et al., 1996), but the evidence for it is marginal and further trials involving these approaches to treat persistent symptoms after a mTBI are required. Another promising option for the after-care of mTBI which could easily combine helpful information and elements from cognitive behavioural therapy would be the use of internet-based treatment. Such internet-based intervention has shown equal beneficial results and even more long term efficacy as face-to-face treatment in a previous study treating depressive patients (Wagner, Horn, & Maercker, 2014).

I could also imagine future studies evaluating the influence of performance testing by means of neuropsychological assessments in the sub-acute phase (> 7 days post-injury) on return to work and persistence of symptoms. From my clinical experience, performance testing allows more realistic estimation of the appearance of symptoms under pressure and can possibly act like exposure therapy to overcome the anxiety from persistent symptoms after mTBI.

From the results of our project, we concluded that SWI seems to be a promising tool in the detection of MB, which have shown predictive strength for pPCS and cognitive outcome. Further studies using SWI in the evaluation of mTBI patients should focus on the detection of MB, on methods to detect MB apart from visual detection such as proposed by Helmer et al. (2014), on the changes of MB over time, and last but not least on the correlation of MB with pPCS, cognitive outcome and other outcome measures such as return to work, as well as the location of MB and cognitive impairment as performed in patients with other pathologies (Chai et al., 2016). Longitudinal studies should include analysis of the number and size of MB, as well as quantitative susceptibility maps between baseline in the acute phase and after a year. It seems probable that MB, regardless of their origin, are a potential risk factor for worse outcome after mTBI and possibly after other disease. Therefore, further investigations in mTBI and patient samples with other disease, as well as with healthy controls, could be performed to gain more knowledge about the cause of MB and their influence on recovery. In addition, the question remains, how much benefit we get from an SWI additional to the evaluation of risk factors in the prognosis of pPCS and delayed return to work.

Our results implicate that the pathological processes as measurable with DTI change from the acute to the chronic phase (one year post-injury) after an mTBI, to gain more insight about the course of physiological recovery further longitudinal studies would be needed. To be able to use DTI in the clinical setting, analysis methods are needed, which allow the analysis and interpretation of an individual patient's scans in a time-efficient manner, otherwise it remains a methodology for scientific purpose.

3.3. General Conclusions

The factors influencing the recovery after mTBI are vast and can probably best be explained with a biopsychosocial model (Iverson, 2012) and it is questioned if they can be captured sufficiently by means of any single diagnostic measure. MRI-scans of mTBI patients could get more interesting for insurance reasons, if future evidence suggests its strength in the discrimination between individuals who suffered a mTBI and such who did not. Future effort should focus on the effectiveness and content of written information given to all patients during their initial introduction in the emergency department or with the general practitioner. More evidence is needed about the recommendation of sick leave after a mTBI, since it is a question each medical doctor treating mTBI patients is faced with. Patients returning to medical care due to persistent complaints should be given contact information of a therapist with experience in

mTBI to receive support (in his practice or over the phone) in the management of symptoms and encouragement for an early return to everyday activities and those kind of follow-ups should be further evaluated.

REFERENCES

Adams, J. H., Graham, D. I., Murray, L. S., & Scott, G. (1982). Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases. *Ann Neurol*, *12*(6), 557–563. doi:10.1002/ana.410120610

Adirim, T. (2007). Concussions in Sports and Recreation. *Clin Ped Emerg Med*. (8), 2–6.

af Geijerstam, J.-L., & Britton, M. (2003). Mild head injury - mortality and complication rate: meta-analysis of findings in a systematic literature review. *Acta neurochirurgica*, *145*(10), 843. doi:10.1007/s00701-003-0115-1

Akoudad, S., Darweesh, S. K., Leening, M. J., Koudstaal, P. J., Hofman, A., van der Lugt, A.,. . . Vernooij, M. W. (2014). Use of coumarin anticoagulants and cerebral microbleeds in the general population. *Stroke*, *45*(11), 3436–3439. doi:10.1161/STROKEAHA.114.007112

Al Sayegh, A., Sandford, D., & Carson, A. J. (2010). Psychological approaches to treatment of postconcussion syndrome: a systematic review. *Journal of neurology, neurosurgery, and psychiatry*, *81*(10), 1128–1134. doi:10.1136/jnnp.2008.170092

Andersson, J. L., Jenkinson, M., & Smith, S. (2007). Non-linear optimisation. FMRIB technical report TR07JA1. *University of Oxford FMRIB Centre: Oxford, UK*.

Arfanakis, K., Haughton, V. M., Carew, J. D., Rogers, B. P., Dempsey, R. J., & Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. *AJNR Am J Neuroradiol*, *23*(5), 794–802.

Barrio-Arranz, G., Luis-Garcia, R. de, Tristan-Vega, A., Martin-Fernandez, M., & Aja-Fernandez, S. (2015). Impact of MR Acquisition Parameters on DTI Scalar Indexes: A Tractography Based Approach. *PLoS One*, *10*(10), e0137905. doi:10.1371/journal.pone.0137905

Bazarian, J., Hartman, M., & Delahunta, E. (2000). Minor head injury: predicting follow-up after discharge from the Emergency Department. *Brain Injury*, *14*(3), 285–294.

Bazarian, J. J., Zhong, J., Blyth, B., Zhu, T., Kavcic, V., & Peterson, D. (2007). Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. *J Neurotrauma*, *24*(9), 1447–1459. doi:10.1089/neu.2007.0241

Bazarian, J. J., Blyth, B., & Cimpello, L. (2006). Bench to Bedside: Evidence for Brain Injury after Concussion-Looking beyond the Computed Tomography Scan. *Academic Emergency Medicine*, *13*(2), 199–214. doi:10.1197/j.aem.2005.07.031

Beauchamp, M. H., Ditchfield, M., Babl, F. E., Kean, M., Catroppa, C., Yeates, K. O., & Anderson, V. (2011). Detecting traumatic brain lesions in children: CT versus MRI versus susceptibility weighted imaging (SWI). *J Neurotrauma*, *28*(6), 915–927. doi:10.1089/neu.2010.1712

Bell, K. R., Hoffman, J. M., Temkin, N. R., Powell, J. M., Fraser, R. T., Esselman, P. C.,. . . Dikmen, S. (2008). The effect of telephone counselling on reducing post-traumatic symptoms after mild traumatic brain injury: a randomised trial. *Journal of neurology, neurosurgery, and psychiatry*, *79*(11), 1275–1281. doi:10.1136/jnnp.2007.141762

Benson, R. R., Meda, S. A., Vasudevan, S., Kou, Z., Govindarajan, K. A., Hanks, R. A.,. . . Haacke, E. M. (2007). Global white matter analysis of diffusion tensor images is predictive of injury severity in traumatic brain injury. *J Neurotrauma*, *24*(3), 446–459. doi:10.1089/neu.2006.0153

Bigler, E. D., & Bazarian, J. J. (2010). Diffusion tensor imaging: a biomarker for mild traumatic brain injury? *Neurology*, *74*(8), 626–627. doi:10.1212/WNL.0b013e3181d3e43a

Bigler, E. D. (2008). Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *Journal of the International Neuropsychological Society : JINS*, *14*(1), 1–22. doi:10.1017/S135561770808017X

Bleiberg, J., Cernich, A. N., Cameron, K., Sun, W., Peck, K., Ecklund, P. J.,. . . Warden, D. L. (2004). Duration of cognitive impairment after sports concussion. *Neurosurgery*, *54*(5), 1073-78; discussion 1078-80.

Boake, C., McCauley, S. R., Levin, H. S., Pedroza, C., Contant, C. F., Song, J. X.,. . . Diaz-Marchan, P. J. (2005). Diagnostic criteria for postconcussional syndrome after mild to moderate traumatic brain injury. *J Neuropsychiatry Clin Neurosci*, *17*(3), 350–356. doi:10.1176/appi.neuropsych.17.3.350

Bouix, S., Pasternak, O., Rathi, Y., Pelavin, P. E., Zafonte, R., & Shenton, M. E. (2013). Increased gray matter diffusion anisotropy in patients with persistent post-concussive symptoms following mild traumatic brain injury. *PLoS One*, *8*(6), e66205. doi:10.1371/journal.pone.0066205

Cancelliere, C., Kristman, V. L., Cassidy, J. D., Hincapie, C. A., Cote, P., Boyle, E.,. . . Borg, J. (2014). Systematic review of return to work after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*, *95*(3 Suppl), 9. doi:10.1016/j.apmr.2013.10.010

Carroll, L., Cassidy, J. D., Holm, L., Kraus, J., & Coronado, V. (2004). Methodological issues and research recommendations for mild traumatic brain injury: The who collaborating centre task force on mild traumatic brain injury. *Journal of Rehabilitation Medicine*, *36*(0), 113–125. doi:10.1080/16501960410023877

Carroll, L., Cassidy, J. D., Peloso, P., Borg, J., Holst, H. von, Holm, L.,. . . Pépin, M. (2004). Prognosis for mild traumatic brain injury: Results of the who collaborating centre task force on mild traumatic brain injury. *Journal of Rehabilitation Medicine*, *36*(0), 84–105. doi:10.1080/16501960410023859

Cassidy, J. D., Carroll, L., Peloso, P., Borg, J., Holst, H. von, Holm, L.,. . . Coronado, V. (2004). Incidence, risk factors and prevention of mild traumatic brain injury: Results of the

who collaborating centre task force on mild traumatic brain injury. *Journal of Rehabilitation Medicine*, *36*(0), 28–60. doi:10.1080/16501960410023732

Chai, C., Wang, Z., Fan, L., Zhang, M., Chu, Z., Zuo, C.,. . . Xia, S. (2016). Increased Number and Distribution of Cerebral Microbleeds Is a Risk Factor for Cognitive Dysfunction in Hemodialysis Patients: A Longitudinal Study. *Medicine*, *95*(12), e2974. doi:10.1097/MD.0000000000002974

Chang, V. H., Lombard, L. A., & Greher, M. R. (2011). Mild Traumatic Brain Injury in the Occupational Setting. *PM&R*, *3*(10), S387-S395. doi:10.1016/j.pmrj.2011.08.007

Chen, J. K., Johnston, K. M., Collie, A., McCrory, P., & Ptito, A. (2007). A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *J Neurol Neurosurg Psychiatry*, *78*(11), 1231–1238. doi:10.1136/jnnp.2006.110395

Chen, J., Jin, H., Zhang, Y., Liang, Q., Liao, H., Guo, Z., & Han, X. (2012). MRS and diffusion tensor image in mild traumatic brain injuries. *Asian Pacific Journal of Tropical Medicine*, *5*(1), 67–70. doi:10.1016/S1995-7645(11)60248-4

Chu, Z., Wilde, E. A., Hunter, J. V., McCauley, S. R., Bigler, E. D., Troyanskaya, M.,. . . Levin, H. S. (2010). Voxel-based analysis of diffusion tensor imaging in mild traumatic brain injury in adolescents. *AJNR Am J Neuroradiol*, *31*(2), 340–346. doi:10.3174/ajnr.A1806

Cubon, V. A., Putukian, M., Boyer, C., & Dettwiler, A. (2011). A diffusion tensor imaging study on the white matter skeleton in individuals with sports-related concussion. *J Neurotrauma*, *28*(2), 189–201. doi:10.1089/neu.2010.1430

Cushman, J. G., Agarwal, N., Fabian, T. C., Garcia, V., Nagy, K. K., Pasquale, M. D., & Salotto, A. G. (2001). Practice Management Guidelines for the Management of Mild Traumatic Brain Injury: The EAST Practice Management Guidelines Work Group. *The*

Journal of Trauma: Injury, Infection, and Critical Care, *51*(5), 1016–1026. doi:10.1097/00005373-200111000-00034

Dall'Acqua, P., Johannes, S., Mica, L., Simmen, H.-P., Glaab, R., Fandino, J.,. . . Hänggi, J. (2016). Connectomic and Surface-Based Morphometric Correlates of Acute Mild Traumatic Brain Injury. *Frontiers in Human Neuroscience*, *10*(915), 394. doi:10.3389/fnhum.2016.00127

Deferoxamine reduces intracerebral hematoma-induced iron accumulation and neuronal death in piglets.

Dikmen, S. S., Temkin, N. R., Machamer, J. E., Holubkov, A. L., Fraser, R. T., & Winn, H. R. (1994). Employment following traumatic head injuries. *Archives of neurology*, *51*(2), 177–186.

Drake, A. I., Gray, N., Yoder, S., Pramuka, M., & Llewellyn, M. (2000). Factors predicting return to work following mild traumatic brain injury: a discriminant analysis. *The Journal of head trauma rehabilitation*, *15*(5), 1103–1112.

Eierud, C., Craddock, R. C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., & LaConte, S. M. (2014). Neuroimaging after mild traumatic brain injury: Review and meta-analysis. *NeuroImage: Clinical*, *4*, 283–294. doi:10.1016/j.nicl.2013.12.009

Eliyahu, L., Kirkland, S., Campbell, S., Rowe, B. H., & Carpenter, C. R. (2016). The effectiveness of early educational interventions in the Emergency Department to reduce incidence or severity of post-concussion syndrome following a concussion: A systematic review. *Academic Emergency Medicine*, n/a-n/a. doi:10.1111/acem.12924

Fakhran, S., Yaeger, K., Collins, M., & Alhilali, L. (2014). Sex differences in white matter abnormalities after mild traumatic brain injury: localization and correlation with outcome. *Radiology*, *272*(3), 815–823. doi:10.1148/radiol.14132512

Faux, S., & Sheedy, J. (2008). A prospective controlled study in the prevalence of posttraumatic headache following mild traumatic brain injury. *Pain Med*, *9*(8), 1001–1011. doi:10.1111/j.1526-4637.2007.00404.x

Faux, S., Sheedy, J., Delaney, R., & Riopelle, R. (2011). Emergency department prediction of post-concussive syndrome following mild traumatic brain injury--an international cross-validation study. *Brain Inj*, *25*(1), 14–22. doi:10.3109/02699052.2010.531686

Friedland, J. F., & Dawson, D. R. (2001). Function after motor vehicle accidents: a prospective study of mild head injury and posttraumatic stress. *The Journal of nervous and mental disease*, *189*(7), 426–434.

Gasparovic, C., Yeo, R., Mannell, M., Ling, J., Elgie, R., Phillips, J.,. . . Mayer, A. R. (2009). Neurometabolite concentrations in gray and white matter in mild traumatic brain injury: an 1H-magnetic resonance spectroscopy study. *J Neurotrauma*, *26*(10), 1635–1643. doi:10.1089/neu.2009-0896

Gautschi, O. P., Frey, S. P., & Zellweger, R. (2007). [Diagnosis and management of patients with mild traumatic brain injury--an update with recommendations and future perspectives]. *Praxis (Bern 1994)*, *96*(3), 53-8; discussion 59-60. doi:10.1024/1661-8157.96.3.53

George, E. O., Roys, S., Sours, C., Rosenberg, J., Zhuo, J., Shanmuganathan, K., & Gullapalli, R. P. (2014). Longitudinal and prognostic evaluation of mild traumatic brain injury: A 1H-magnetic resonance spectroscopy study. *J Neurotrauma*, *31*(11), 1018–1028. doi:10.1089/neu.2013.3224

Gioia, G. A., Collins, M., & Isquith, P. K. (2008). Improving identification and diagnosis of mild traumatic brain injury with evidence: psychometric support for the acute concussion evaluation. *J Head Trauma Rehabil*, *23*(4), 230–242. doi:10.1097/01.HTR.0000327255.38881.ca

Giza, C. C., & Hovda, D. A. (2001). The Neurometabolic Cascade of Concussion. *J Athl Train*, *36*(3), 228–235.

Giza, C. C., & Hovda, D. A. (2014). The new neurometabolic cascade of concussion. *Neurosurgery*, *75 Suppl 4*, 33. doi:10.1227/NEU.0000000000000505

Gronwall, D. (1986). Rehabilitation programs for patients with mild head injury: components, problems, and evaluation. *The Journal of head trauma rehabilitation*, *1*(2), 53–62.

Guskiewicz, K. M., Bruce, S. L., Cantu, R. C., Ferrara, M. S., Kelly, J. P., McCrea, M.,. . . Valovich McLeod, T. C. (2004). National Athletic Trainers' Association Position Statement: Management of Sport-Related Concussion. *J Athl Train*, *39*(3), 280–297.

Haacke, E. M., Xu, Y., Cheng, Y.-C. N., & Reichenbach, J. R. (2004). Susceptibility weighted imaging (SWI). *Magnetic resonance in medicine*, *52*(3), 612–618. doi:10.1002/mrm.20198

Haboubi, N. H., Long, J., Koshy, M., & Ward, A. B. (2001). Short-term sequelae of minor head injury (6 years experience of minor head injury clinic). *Disability and Rehabilitation*, *23*(14), 635–638.

Helmer, K. G., Pasternak, O., Fredman, E., Preciado, R. I., Koerte, I. K., Sasaki, T.,. . . Echlin, P. S. (2014). Hockey Concussion Education Project, Part 1. Susceptibility-weighted imaging study in male and female ice hockey players over a single season. *Journal of neurosurgery*, *120*(4), 864–872. doi:10.3171/2013.12.JNS132093

Henry, L. C., Tremblay, S., Leclerc, S., Khiat, A., Boulanger, Y., Ellemberg, D., & Lassonde, M. (2011). Metabolic changes in concussed American football players during the acute and chronic post-injury phases. *BMC Neurol*, *11*, 105. doi:10.1186/1471-2377-11-105

Henry, L. C., Tremblay, S., Boulanger, Y., Ellemberg, D., & Lassonde, M. (2010). Neurometabolic Changes in the Acute Phase after Sports Concussions Correlate with Symptom Severity. *Journal of Neurotrauma*, *27*(1), 65–76. doi:10.1089/neu.2009.0962

Hinkle, J. L., Alves, W. M., Rimell, R. W., & Jane, J. A. (1986). Restoring social competence in minor head-injury patients. *The Journal of neuroscience nursing : journal of the American Association of Neuroscience Nurses*, *18*(5), 268–271.

Hodgson, J., McDonald, S., Tate, R., & Gertler, P. (2005). A Randomised Controlled Trial of a Cognitive-Behavioural Therapy Program for Managing Social Anxiety After Acquired Brain Injury. *Brain Impairment*, *6*(03), 169–180. doi:10.1375/brim.2005.6.3.169

Hou, R., Moss-Morris, R., Peveler, R., Mogg, K., Bradley, B. P., & Belli, A. (2012). When a minor head injury results in enduring symptoms: a prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury. *J Neurol Neurosurg Psychiatry*, *83*(2), 217–223. doi:10.1136/jnnp-2011-300767

Huang, Y. L., Kuo, Y. S., Tseng, Y. C., Chen, D. Y., Chiu, W. T., & Chen, C. J. (2015). Susceptibility-weighted MRI in mild traumatic brain injury. *Neurology*, *84*(6), 580–585. doi:10.1212/WNL.0000000000001237

Hughes, D. G., Jackson, A., Mason, D. L., Berry, E., Hollis, S., & Yates, D. W. (2004). Abnormalities on magnetic resonance imaging seen acutely following mild traumatic brain injury: correlation with neuropsychological tests and delayed recovery. *Neuroradiology*, *46*(7), 550–558. doi:10.1007/s00234-004-1227-x

Huisman, T. A., Schwamm, L. H., Schaefer, P. W., Koroshetz, W. J., Shetty-Alva, N., Ozsunar, Y.,. . . Sorensen, A. G. (2004). Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *AJNR Am J Neuroradiol*, *25*(3), 370–376.

Inglese, M., Makani, S., Johnson, G., Cohen, B. A., Silver, J. A., Gonen, O., & Grossman, R. I. (2005). Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg*, *103*(2), 298–303. doi:10.3171/jns.2005.103.2.0298

Iverson, G. L. (2005). Outcome from mild traumatic brain injury. *Curr Opin Psychiatry*, *18*(3), 301–317. doi:10.1097/01.yco.0000165601.29047.ae

Iverson, G. L. (2012). A biopsychosocial conceptualization of poor outcome from mild traumatic brain injury. *PTSD and mild traumatic brain injury*, 37–60.

Iverson, G. L., Lange, R. T., Wäljas, M., Liimatainen, S., Dastidar, P., Hartikainen, K. M.,. . . Ohman, J. (2012). Outcome from Complicated versus Uncomplicated Mild Traumatic Brain Injury. *Rehabilitation research and practice*, *2012*, 415740. doi:10.1155/2012/415740

Jarrett, M., Tam, R., Hernández-Torres, E., Martin, N., Perera, W., Zhao, Y.,. . . Rauscher, A. (2016). A Prospective Pilot Investigation of Brain Volume, White Matter Hyperintensities, and Hemorrhagic Lesions after Mild Traumatic Brain Injury. *Frontiers in neurology*, *7*, 11. doi:10.3389/fneur.2016.00011

Karr, J. E., Areshenkoff, C. N., & Garcia-Barrera, M. A. (2014). The neuropsychological outcomes of concussion: a systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. *Neuropsychology*, *28*(3), 321–336. doi:10.1037/neu0000037

Kim, B. J., & Lee, S. H. (2015). Prognostic Impact of Cerebral Small Vessel Disease on Stroke Outcome. *J Stroke*, *17*(2), 101–110. doi:10.5853/jos.2015.17.2.101

Kim, N., Branch, C. A., Kim, M., & Lipton, M. L. (2013). Whole brain approaches for identification of microstructural abnormalities in individual patients: comparison of techniques applied to mild traumatic brain injury. *PloS one*, *8*(3), e59382. doi:10.1371/journal.pone.0059382

King, N. S. (2003). Post-concussion syndrome: clarity amid the controversy? *Br J Psychiatry*, *183*, 276–278.

Kinnunen, K. M., Greenwood, R., Powell, J. H., Leech, R., Hawkins, P. C., Bonnelle, V.,. . . Sharp, D. J. (2011). White matter damage and cognitive impairment after traumatic brain injury. *Brain*, *134*(Pt 2), 449–463. doi:10.1093/brain/awq347

Kirov, I., Fleysher, L., Babb, J. S., Silver, J. M., Grossman, R. I., & Gonen, O. (2007). Characterizing 'mild' in traumatic brain injury with proton MR spectroscopy in the thalamus: Initial findings. *Brain Inj*, *21*(11), 1147–1154. doi:10.1080/02699050701630383

Kirov, I., Tal, A., Babb, J. S., Reaume, J., Bushnik, T., Ashman, T. A.,. . . Gonen, O. (2013). Proton MR spectroscopy correlates diffuse axonal abnormalities with post-concussive symptoms in mild traumatic brain injury. *J Neurotrauma*, *30*(13), 1200–1204. doi:10.1089/neu.2012.2696

Korn, A., Golan, H., Melamed, I., Pascual-Marqui, R., & Friedman, A. (2005). Focal cortical dysfunction and blood-brain barrier disruption in patients with Postconcussion syndrome. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society*, *22*(1), 1–9.

Kou, Z., Gattu, R., Kobeissy, F., Welch, R. D., O'Neil, B. J., Woodard, J. L.,. . . Mondello, S. (2013). Combining biochemical and imaging markers to improve diagnosis and characterization of mild traumatic brain injury in the acute setting: results from a pilot study. *PLoS One*, *8*(11), e80296. doi:10.1371/journal.pone.0080296

Kraus, M. F., Susmaras, T., Caughlin, B. P., Walker, C. J., Sweeney, J. A., & Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain*, *130*(Pt 10), 2508–2519. doi:10.1093/brain/awm216

Kristman, V. L., Cote, P., Hogg-Johnson, S., Cassidy, J. D., van Eerd, D., Vidmar, M.,. . . Wennberg, R. A. (2010). The Burden of Work Disability Associated with Mild Traumatic Brain Injury in Ontario Compensated Workers: A Prospective Cohort Study~!2009-11-16~!2010-02-21~!2010-03-16~! *The Open Occupational Health & Safety Journal*, *2*(1), 1–8. doi:10.2174/1876216601002010001

Kruijk, J. R. de, Twijnstra, A., Meerhoff, S., & Leffers, P. (2001). Management of mild traumatic brain injury: lack of consensus in Europe. *Brain Inj*, *15*(2), 117–123. doi:10.1080/026990501458353

Kumar, R., Husain, M., Gupta, R. K., Hasan, K. M., Haris, M., Agarwal, A. K.,. . . Narayana, P. A. (2009). Serial changes in the white matter diffusion tensor imaging metrics in moderate traumatic brain injury and correlation with neuro-cognitive function. *J Neurotrauma*, *26*(4), 481–495. doi:10.1089/neu.2008.0461

Kumar, S., Rao, S. L., Chandramouli, B. A., & Pillai, S. V. (2009). Reduction of Functional Brain Connectivity in Mild Traumatic Brain Injury during Working Memory. *Journal of Neurotrauma*, 090330061141047. doi:10.1089/neu.2008-0644

Lange, R. T., Panenka, W. J., Shewchuk, J. R., Heran, M. K. S., Brubacher, J. R., Bioux, S.,. . . Iverson, G. L. (2015). Diffusion Tensor Imaging Findings and Postconcussion Symptom Reporting Six Weeks Following Mild Traumatic Brain Injury. *Archives of Clinical Neuropsychology*, *30*(1), 7–25. doi:10.1093/arclin/acu060

Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: concepts and applications. *Journal of magnetic resonance imaging : JMRI*, *13*(4), 534–546.

Lee, H., Wintermark, M., Gean, A. D., Ghajar, J., Manley, G. T., & Mukherjee, P. (2008). Focal lesions in acute mild traumatic brain injury and neurocognitive outcome: CT versus 3T MRI. *J Neurotrauma*, *25*(9), 1049–1056. doi:10.1089/neu.2008.0566

Levin, H. S., & Diaz-Arrastia, R. R. (2015). Diagnosis, prognosis, and clinical management of mild traumatic brain injury. *The Lancet Neurology*, *14*(5), 506–517. doi:10.1016/S1474-4422(15)00002-2

Lipton, M. L., Gellella, E., Lo, C., Gold, T., Ardekani, B. A., Shifteh, K.,. . . Branch, C. A. (2008). Multifocal white matter ultrastructural abnormalities in mild traumatic brain injury

with cognitive disability: a voxel-wise analysis of diffusion tensor imaging. *J Neurotrauma*, *25*(11), 1335–1342. doi:10.1089/neu.2008.0547

Liu, G., Ghimire, P., Pang, H., Wu, G., & Shi, H. (2015). Improved sensitivity of 3.0 Tesla susceptibility-weighted imaging in detecting traumatic bleeds and its use in predicting outcomes in patients with mild traumatic brain injury. *Acta Radiol*, *56*(10), 1256–1263. doi:10.1177/0284185114552883

Liu, W., Soderlund, K., Senseney, J. S., Joy, D., Yeh, P.-H., Ollinger, J.,. . . Riedy, G. (2016). Imaging Cerebral Microhemorrhages in Military Service Members with Chronic Traumatic Brain Injury. *Radiology*, *278*(2), 536–545. doi:10.1148/radiol.2015150160

Losoi, H., Silverberg, N., Waljas, M., Turunen, S., Rosti-Otajarvi, E., Helminen, M.,. . . Iverson, G. L. (2015). Recovery from Mild Traumatic Brain Injury in Previously Healthy Adults. *J Neurotrauma.* doi:10.1089/neu.2015.4070

Maestas, K. L., Sander, A. M., Clark, A. N., van Veldhoven, L. M., Struchen, M. A., Sherer, M., & Hannay, H. J. (2014). Preinjury coping, emotional functioning, and quality of life following uncomplicated and complicated mild traumatic brain injury. *The Journal of head trauma rehabilitation*, *29*(5), 407–417. doi:10.1097/HTR.0b013e31828654b4

Majerske, C. W., Mihalik, J. P., Ren, D., Collins, M. W., Reddy, C. C., Lovell, M. R., & Wagner, A. K. (2008). Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. *J Athl Train*, *43*(3), 265–274. doi:10.4085/1062-6050-43.3.265

Management of Concussion/mTBI Working Group. (2009). VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury. *Journal of rehabilitation research and development*, *46*(6), 68.

Maroon, J. C., Lovell, M. R., Norwig, J., Podell, K., Powell, J. W., & Hartl, R. (2000). Cerebral concussion in athletes: evaluation and neuropsychological testing. *Neurosurgery*, *47*(3), 659-69; discussion 669-72.

Marshall, S., Bayley, M., McCullagh, S., Velikonja, D., Berrigan, L., Ouchterlony, D., & Weegar, K. (2015). Updated clinical practice guidelines for concussion/mild traumatic brain injury and persistent symptoms. *Brain Inj*, *29*(6), 688–700. doi:10.3109/02699052.2015.1004755

Maruta, J., Lee, S. W., Jacobs, E. F., & Ghajar, J. (2010). A unified science of concussion. *Ann N Y Acad Sci*, *1208*, 58–66. doi:10.1111/j.1749-6632.2010.05695.x

Mayer, A. R., Ling, J., Mannell, M. V., Gasparovic, C., Phillips, J. P., Doezema, D.,. . . Yeo, R. A. (2010). A prospective diffusion tensor imaging study in mild traumatic brain injury. *Neurology*, *74*(8), 643–650. doi:10.1212/WNL.0b013e3181d0ccdd

McCrea, M., Guskiewicz, K. M., Marshall, S. W., Barr, W., Randolph, C., Cantu, R. C.,. . . Kelly, J. P. (2003). Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA*, *290*(19), 2556–2563. doi:10.1001/jama.290.19.2556

McCrea, M., Pliskin, N., Barth, J., Cox, D., Fink, J., French, L.,. . . Yoash-Gantz, R. (2008). Official position of the military TBI task force on the role of neuropsychology and rehabilitation psychology in the evaluation, management, and research of military veterans with traumatic brain injury. *Clin Neuropsychol*, *22*(1), 10–26. doi:10.1080/13854040701760981

McCrory, P., Makdissi, M., Davis, G., & Collie, A. (2005). Value of neuropsychological testing after head injuries in football. *Br J Sports Med*, *39 Suppl 1*, 63. doi:10.1136/bjsm.2005.020776

Medana, I. M., & Esiri, M. M. (2003). Axonal damage: a key predictor of outcome in human CNS diseases. *Brain*, *126*(Pt 3), 515–530.

Meier, T. B., Brummel, B. J., Singh, R., Nerio, C. J., Polanski, D. W., & Bellgowan, P. S. (2014). The underreporting of self-reported symptoms following sports-related concussion. *J Sci Med Sport.* doi:10.1016/j.jsams.2014.07.008

Messe, A., Caplain, S., Paradot, G., Garrigue, D., Mineo, J. F., Soto Ares, G.,. . . Lehericy, S. (2011). Diffusion tensor imaging and white matter lesions at the subacute stage in mild traumatic brain injury with persistent neurobehavioral impairment. *Hum Brain Mapp*, *32*(6), 999–1011. doi:10.1002/hbm.21092

Messe, A., Caplain, S., Pelegrini-Issac, M., Blancho, S., Levy, R., Aghakhani, N.,. . . Lehericy, S. (2013). Specific and evolving resting-state network alterations in post-concussion syndrome following mild traumatic brain injury. *PLoS One*, *8*(6), e65470. doi:10.1371/journal.pone.0065470

Miles, L., Grossman, R. I., Johnson, G., Babb, J. S., Diller, L., & Inglese, M. (2008). Short-term DTI predictors of cognitive dysfunction in mild traumatic brain injury. *Brain Inj*, *22*(2), 115–122. doi:10.1080/02699050801888816

Minderhoud, J. M., Boelens, M. E., Huizenga, J., & Saan, R. J. (1980). Treatment of minor head injuries. *Clinical neurology and neurosurgery*, *82*(2), 127–140.

Mittenberg, W. (1996). Cognitive-behavioral prevention of postconcussion syndrome. *Archives of Clinical Neuropsychology*, *11*(2), 139–145. doi:10.1016/0887-6177(95)00006-2

Mittenberg, W., Tremont, G., Zielinski, R. E., Fichera, S., & Rayls, K. R. (1996). Cognitive-behavioral prevention of postconcussion syndrome. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists*, *11*(2), 139–145.

Moore, M., Winkelman, A., Kwong, S., Segal, S. P., Manley, G. T., & Shumway, M. (2014). The emergency department social work intervention for mild traumatic brain injury (SWIFT-Acute): a pilot study. *Brain Injury*, *28*(4), 448–455. doi:10.3109/02699052.2014.890746

Mori, S., & Zhang, J. (2006). Principles of Diffusion Tensor Imaging and Its Applications to Basic Neuroscience Research. *Neuron*, *51*(5), 527–539. doi:10.1016/j.neuron.2006.08.012

MTBI Guidelines Development Team. (2010). *Guidelines for mild traumatic brain injury and persistent symptoms*. Toronto, ON.

Murugavel, M., Cubon, V., Putukian, M., Echemendia, R., Cabrera, J., Osherson, D., & Dettwiler, A. (2014). A longitudinal diffusion tensor imaging study assessing white matter fiber tracts after sports-related concussion. *J Neurotrauma*, *31*(22), 1860–1871. doi:10.1089/neu.2014.3368

Narayana, P. A., Yu, X., Hasan, K. M., Wilde, E. A., Levin, H. S., Hunter, J. V.,. . . McCarthy, J. J. (2015). Multi-modal MRI of mild traumatic brain injury. *Neuroimage Clin*, *7*, 87–97. doi:10.1016/j.nicl.2014.07.010

New South Wales Motor Accident Authority. (2008). *Guidelines for mild traumatic brain injury following closed head injury, Sydney, Australia*. Sydney, Australia.

Niogi, S. N., & Mukherjee, P. (2010). Diffusion tensor imaging of mild traumatic brain injury. *J Head Trauma Rehabil*, *25*(4), 241–255. doi:10.1097/HTR.0b013e3181e52c2a

Niogi, S. N., Mukherjee, P., Ghajar, J., Johnson, C. E., Kolster, R., Lee, H.,. . . McCandliss, B. D. (2008). Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. *Brain*, *131*(Pt 12), 3209–3221. doi:10.1093/brain/awn247

Niogi, S. N., Mukherjee, P., Ghajar, J., Johnson, C., Kolster, R. A., Sarkar, R.,. . . McCandliss, B. D. (2008). Extent of microstructural white matter injury in postconcussive

syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. *AJNR Am J Neuroradiol*, *29*(5), 967–973. doi:10.3174/ajnr.A0970

Nolin, P., & Heroux, L. (2006). Relations among sociodemographic, neurologic, clinical, and neuropsychologic variables, and vocational status following mild traumatic brain injury: a follow-up study. *The Journal of head trauma rehabilitation*, *21*(6), 514–526.

Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2.

Ownsworth, T., & McKenna, K. (2004). Investigation of factors related to employment outcome following traumatic brain injury: a critical review and conceptual model. *Disability and Rehabilitation*, *26*(13), 765–783. doi:10.1080/09638280410001696700

Park, J. H., Park, S. W., Kang, S. H., Nam, T. K., Min, B. K., & Hwang, S. N. (2009). Detection of traumatic cerebral microbleeds by susceptibility-weighted image of MRI. *J Korean Neurosurg Soc*, *46*(4), 365–369. doi:10.3340/jkns.2009.46.4.365

Paterakis, K., Karantanas, A. H., Komnos, A., & Volikas, Z. (2000). Outcome of patients with diffuse axonal injury: the significance and prognostic value of MRI in the acute phase. *J Trauma*, *49*(6), 1071–1075.

Pertab, J. L., James, K. M., & Bigler, E. D. (2009). Limitations of mild traumatic brain injury meta-analyses. *Brain Inj*, *23*(6), 498–508. doi:10.1080/02699050902927984

Ponsford, J., Cameron, P., Fitzgerald, M., Grant, M., & Mikocka-Walus, A. (2011). Long term outcomes after uncomplicated mild traumatic brain injury: A comparison with trauma controls.

Ponsford, J., Willmott, C., Rothwell, A., Cameron, P., Kelly, A.-M., Nelms, R., & Curran, C. (2002). Impact of early intervention on outcome following mild head injury in adults. *Journal of neurology, neurosurgery, and psychiatry*, *73*(3), 330–332.

Ponsford, J., Willmott, C., Rothwell, A., Cameron, P., Kelly, A., Nelms, R.,. . . NG, K. I. (2000). Factors influencing outcome following mild traumatic brain injury in adults. *Journal of the International Neuropsychological Society*, *6*(5), 568–579. doi:10.1017/S1355617700655066

Ptak, T., Sheridan, R. L., Rhea, J. T., Gervasini, A. A., Yun, J. H., Curran, M. A.,. . . Novelline, R. A. (2003). Cerebral fractional anisotropy score in trauma patients: a new indicator of white matter injury after trauma. *AJR Am J Roentgenol*, *181*(5), 1401–1407. doi:10.2214/ajr.181.5.1811401

Quantification of iron in the non-human primate brain with diffusion-weighted magnetic resonance imaging.

Relander, M., Troupp, H., & Af Bjorkesten, G. (1972). Controlled trial of treatment for cerebral concussion. *British medical journal*, *4*(5843), 777–779.

Reynolds, S., Paniak, C., Toller-Lobe, G., & Nagy, J. (2003). A Longitudinal Study of Compensation-Seeking and Return to Work in a Treated Mild Traumatic Brain Injury Sample. *Journal of Head Trauma Rehabilitation*, *18*(2), 139–147. doi:10.1097/00001199-200303000-00005

Rueckert, D., Sonoda, L. I., Hayes, C., Hill, D. L., Leach, M. O., & Hawkes, D. J. (1999). Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging*, *18*(8), 712–721. doi:10.1109/42.796284

Rugg-Gunn, F. J. (2001). Diffusion imaging shows abnormalities after blunt head trauma when conventional magnetic resonance imaging is normal. *Journal of Neurology, Neurosurgery & Psychiatry*, *70*(4), 530–533. doi:10.1136/jnnp.70.4.530

Rutgers, D. R., Toulgoat, F., Cazejust, J., Fillard, P., Lasjaunias, P., & Ducreux, D. (2008). White matter abnormalities in mild traumatic brain injury: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*, *29*(3), 514–519. doi:10.3174/ajnr.A0856

Ryan, L. M., & Warden, D. L. (2003). Post concussion syndrome. *Int Rev Psychiatry*, *15*(4), 310–316. doi:10.1080/09540260310001606692

Sbordone, R. J. (2001). Limitations of neuropsychological testing to predict the cognitive and behavioral functioning of persons with brain injury in real-world settings. *NeuroRehabilitation*, *16*(4), 199–201.

Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative diseases target large-scale human brain networks. *Neuron*, *62*(1), 42–52. doi:10.1016/j.neuron.2009.03.024

Sharp, D. J., & Ham, T. E. (2011). Investigating white matter injury after mild traumatic brain injury. *Curr Opin Neurol*, *24*(6), 558–563. doi:10.1097/WCO.0b013e32834cd523

Sheedy, J., Geffen, G., Donnelly, J., & Faux, S. (2006). Emergency department assessment of mild traumatic brain injury and prediction of post-concussion symptoms at one month post injury. *J Clin Exp Neuropsychol*, *28*(5), 755–772. doi:10.1080/13803390591000864

Shenton, M. E., Hamoda, H. M., Schneiderman, J. S., Bouix, S., Pasternak, O., Rathi, Y.,. . . Zafonte, R. (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging Behav*, *6*(2), 137–192. doi:10.1007/s11682-012-9156-5

Shumskaya, E., Andriessen, T. M., Norris, D. G., & Vos, P. E. (2012). Abnormal whole-brain functional networks in homogeneous acute mild traumatic brain injury. *Neurology*, *79*(2), 175–182. doi:10.1212/WNL.0b013e31825f04fb

Silverberg, N. D., & Iverson, G. L. (2013). Is rest after concussion "the best medicine?: ": recommendations for activity resumption following concussion in athletes, civilians, and military service members. *J Head Trauma Rehabil*, *28*(4), 250–259. doi:10.1097/HTR.0b013e31825ad658

Slobounov, S. M., Zhang, K., Pennell, D., Ray, W., Johnson, B., & Sebastianelli, W. (2010). Functional abnormalities in normally appearing athletes following mild traumatic brain injury: a functional MRI study. *Exp Brain Res*, *202*(2), 341–354. doi:10.1007/s00221-009-2141-6

Smith, S. M. (2002). Fast robust automated brain extraction. *Hum Brain Mapp*, *17*(3), 143–155. doi:10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E.,. . . Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*, *31*(4), 1487–1505. doi:10.1016/j.neuroimage.2006.02.024

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H.,. . . Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23 Suppl 1*, 19. doi:10.1016/j.neuroimage.2004.07.051

Smits, M., Houston, G. C., Dippel, D. W., Wielopolski, P. A., Vernooij, M. W., Koudstaal, P. J.,. . . van der Lugt, A. (2011). Microstructural brain injury in post-concussion syndrome after minor head injury. *Neuroradiology*, *53*(8), 553–563. doi:10.1007/s00234-010-0774-6

Snell, D. L., Siegert, R. J., Hay-Smith, E. J., & Surgenor, L. J. (2011). Associations between illness perceptions, coping styles and outcome after mild traumatic brain injury: preliminary results from a cohort study. *Brain Inj*, *25*(11), 1126–1138. doi:10.3109/02699052.2011.607786

Soares, J. M., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. *Frontiers in neuroscience*, *7*, 31. doi:10.3389/fnins.2013.00031

Son, B. C., Park, C. K., Choi, B. G., Kim, E. N., Choe, B. Y., Lee, K. S.,. . . Kang, J. K. (2000). Metabolic changes in pericontusional oedematous areas in mild head injury evaluated by 1H MRS. *Acta Neurochir Suppl, 76*, 13–16.

Spitz, G., Maller, J. J., Ng, A., O'Sullivan, R., Ferris, N. J., & Ponsford, J. L. (2013). Detecting lesions after traumatic brain injury using susceptibility weighted imaging: a comparison with fluid-attenuated inversion recovery and correlation with clinical outcome. *J Neurotrauma, 30*(24), 2038–2050. doi:10.1089/neu.2013.3021

Sterr, A., Herron, K. A., Hayward, C., & Montaldi, D. (2006). Are mild head injuries as mild as we think?: Neurobehavioral concomitants of chronic post-concussion syndrome. *BMC Neurol, 6*, 7. doi:10.1186/1471-2377-6-7

Stiell, I. G., Wells, G. A., Vandemheen, K., Clement, C., Lesiuk, H., Laupacis, A.,. . . Worthington, J. (2001). The Canadian CT Head Rule for patients with minor head injury. *Lancet (London, England), 357*(9266), 1391–1396.

Stokum, J. A., Sours, C., Zhuo, J., Kane, R., Shanmuganathan, K., & Gullapalli, R. P. (2015). A longitudinal evaluation of diffusion kurtosis imaging in patients with mild traumatic brain injury. *Brain Inj, 29*(1), 47–57. doi:10.3109/02699052.2014.947628

Studerus-Germann, A. M., Engel, D. C., Bontempi, P., Thiran, J. P., Daducci, A., Romascano, D.,. . . Hildebrandt, G., & Gautschi, O. P. (2016). Central nervous system microbleeds in the acute phase predict structural integrity in the late phase after mild traumatic brain injury: a longitudinal study with a one year follow-up. *Manuscript submitted for publication (copy on file with author).*

Studerus-Germann, A. M., Engel, D. C., Stienen, M. N., Ow, D. von, & Hildebrandt, G., & Gautschi, O. P. (2016). Three versus seven days to return-to-work after mild traumatic brain injury: a randomised parallel-group trial with neuropsychological assessment. *Manuscript submitted for publication (copy on file with author).*

Studerus-Germann, A. M., Thiran, J. P., & Daducci, A., & Gautschi, O. P. (2016). Diagnostic approaches to predict persistent post-traumatic symptoms after mild traumatic brain injury - a literature review. *Int J Neurosci, 126*(4), 289–298. doi:10.3109/00207454.2015.1033620

Stulemeijer, M., van der Werf, S., Borm, G. F., & Vos, P. E. (2008). Early prediction of favourable recovery 6 months after mild traumatic brain injury. *Journal of Neurology, Neurosurgery & Psychiatry, 79*(8), 936–942. doi:10.1136/jnnp.2007.131250

Styrke, J., Stålnacke, B.-M., Sojka, P., & Björnstig, U. (2007). Traumatic brain injuries in a well-defined population: epidemiological aspects and severity. *Journal of Neurotrauma, 24*(9), 1425–1436. doi:10.1089/neu.2007.0266

Terry, D. P., Faraco, C. C., Smith, D., Diddams, M. J., Puente, A. N., & Miller, L. S. (2012). Lack of long-term fMRI differences after multiple sports-related concussions. *Brain Inj, 26*(13-14), 1684–1696. doi:10.3109/02699052.2012.722259

Tiersky, L. A., Anselmi, V., Johnston, M. V., Kurtyka, J., Roosen, E., Schwartz, T., & Deluca, J. (2005). A trial of neuropsychologic rehabilitation in mild-spectrum traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 86*(8), 1565–1574. doi:10.1016/j.apmr.2005.03.013

Tong, K. A., Ashwal, S., Holshouser, B. A., Nickerson, J. P., Wall, C. J., Shutter, L. A.,. . . Kido, D. (2004). Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. *Ann Neurol, 56*(1), 36–50. doi:10.1002/ana.20123

Tong, K. A., Ashwal, S., Obenaus, A., Nickerson, J. P., Kido, D., & Haacke, E. M. (2008). Susceptibility-weighted MR imaging: a review of clinical applications in children. *AJNR Am J Neuroradiol, 29*(1), 9–17. doi:10.3174/ajnr.A0786

Topal, N. B., Hakyemez, B., Erdogan, C., Bulut, M., Koksal, O., Akkose, S.,. . . Korfali, E. (2008). MR imaging in the detection of diffuse axonal injury with mild traumatic brain injury. *Neurol Res*, *30*(9), 974–978. doi:10.1179/016164108X323799

Toth, A. (2015). Magnetic Resonance Imaging Application in the Area of Mild and Acute Traumatic Brain Injury: Implications for Diagnostic Markers? In F. H. Kobeissy (Ed.), *Frontiers in Neuroengineering. Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects.* Boca Raton (FL).

Toth, A., Kovacs, N., Perlaki, G., Orsi, G., Aradi, M., Komaromy, H.,. . . Schwarcz, A. (2013). Multi-modal magnetic resonance imaging in the acute and sub-acute phase of mild traumatic brain injury: can we see the difference? *J Neurotrauma*, *30*(1), 2–10. doi:10.1089/neu.2012.2486

Vagnozzi, R., Signoretti, S., Tavazzi, B., Floris, R., Ludovici, A., Marziali, S.,. . . Lazzarino, G. (2008). Temporal window of metabolic brain vulnerability to concussion: a pilot 1H-magnetic resonance spectroscopic study in concussed athletes--part III. *Neurosurgery*, *62*(6), 1286-95; discussion 1295-6. doi:10.1227/01.neu.0000333300.34189.74

van der Naalt, J. (2001). Prediction of outcome in mild to moderate head injury: a review. *J Clin Exp Neuropsychol*, *23*(6), 837–851. doi:10.1076/jcen.23.6.837.1018

van der Naalt, J., van Zomeren, A. H., Sluiter, W. J., & Minderhoud, J. M. (1999). One year outcome in mild to moderate head injury: the predictive value of acute injury characteristics related to complaints and return to work. *Journal of neurology, neurosurgery, and psychiatry*, *66*(2), 207–213.

Veeramuthu, V., Narayanan, V., Kuo, T. L., Delano-Wood, L., Chinna, K., Bondi, M. W.,. . . Ramli, N. (2015a). Diffusion Tensor Imaging Parameters in Mild Traumatic Brain Injury and Its Correlation with Early Neuropsychological Impairment: A Longitudinal Study. *J Neurotrauma*, *32*(19), 1497–1509. doi:10.1089/neu.2014.3750

Veeramuthu, V., Narayanan, V., Kuo, T. L., Delano-Wood, L., Chinna, K., Bondi, M. W.,. . . Ramli, N. (2015b). Diffusion Tensor Imaging Parameters in Mild Traumatic Brain Injury and Its Correlation with Early Neuropsychological Impairment: A Longitudinal Study. *J Neurotrauma*, *32*(19), 1497–1509. doi:10.1089/neu.2014.3750

Velikonja, D., Warriner, E. M., Coulson, S., & Brum, C. (2013). The relationship between coping styles and affective/behavioural symptoms among individuals with an acquired brain injury. *Brain Inj*, *27*(2), 158–168. doi:10.3109/02699052.2012.729289

Vikane, E., Hellstrøm, T., Røe, C., Bautz-Holter, E., Aßmus, J., & Skouen, J. S. (2016). Predictors for Return to Work in Subjects with Mild Traumatic Brain Injury. *Behavioural Neurology*, *2016*(4), 1–10. doi:10.1155/2016/8026414

von Wild, K R H. (2008). Posttraumatic rehabilitation and one year outcome following acute traumatic brain injury (TBI): data from the well defined population based German Prospective Study 2000-2002. *Acta neurochirurgica. Supplement*, *101*, 55–60.

Vos, P. E., Battistin, L., Birbamer, G., Gerstenbrand, F., Potapov, A., Prevec, T.,. . . Wild, K. von. (2002). EFNS guideline on mild traumatic brain injury: report of an EFNS task force. *European Journal of Neurology*, *9*(3), 207–219.

Wade, D. T., King, N. S., Wenden, F. J., Crawford, S., & Caldwell, F. E. (1998). Routine follow up after head injury: a second randomised controlled trial. *J Neurol Neurosurg Psychiatry*, *65*(2), 177–183.

Wagner, B., Horn, A. B., & Maercker, A. (2014). Internet-based versus face-to-face cognitive-behavioral intervention for depression: a randomized controlled non-inferiority trial. *Journal of affective disorders*, *152-154*, 113–121. doi:10.1016/j.jad.2013.06.032

Waljas, M., Iverson, G., Lange, R., Hakulinen, U., Dastidar, P., Huhtala, H.,. . . Ohman, J. (2014). A Prospective Biopsychosocial Study of the Persistent Post-Concussion Symptoms Following Mild Traumatic Brain Injury. *J Neurotrauma.* doi:10.1089/neu.2014.3339

Wallesch, C.-W., Curio, N., Kutz, S., Jost, S., Bartels, C., & Synowitz, H. (2001). Outcome after mild-to-moderate blunt head injury: Effects of focal lesions and diffuse axonal injury. *Brain Injury*, *15*(5), 401–412. doi:10.1080/02699050010005959

Wang, J. Y., Bakhadirov, K., Abdi, H., Devous, M. D., Marquez de la Plata, C D, Moore, C.,. . . Diaz-Arrastia, R. (2011). Longitudinal changes of structural connectivity in traumatic axonal injury. *Neurology*, *77*(9), 818–826. doi:10.1212/WNL.0b013e31822c61d7

Wilde, E. A., Hunter, J. V., & Bigler, E. D. (2012). A primer of neuroimaging analysis in neurorehabilitation outcome research. *NeuroRehabilitation*, *31*(3), 227–242. doi:10.3233/NRE-2012-0793

Wilde, E. A., McCauley, S. R., Chu, Z., Hunter, J. V., Bigler, E. D., Yallampalli, R.,. . . Levin, H. S. (2009). Diffusion tensor imaging of hemispheric asymmetries in the developing brain. *J Clin Exp Neuropsychol*, *31*(2), 205–218. doi:10.1080/13803390802098118

Willer, B., & Leddy, J. J. (2006). Management of concussion and post-concussion syndrome. *Curr Treat Options Neurol*, *8*(5), 415–426.

Wright, D. W. (2008). Concussion management for the emergency clinician. *Pract J Emerg Physicians*, *29*, 313–324.

Wu, T. C., Wilde, E. A., Bigler, E. D., Yallampalli, R., McCauley, S. R., Troyanskaya, M.,. . . Levin, H. S. (2010). Evaluating the relationship between memory functioning and cingulum bundles in acute mild traumatic brain injury using diffusion tensor imaging. *J Neurotrauma*, *27*(2), 303–307. doi:10.1089/neu.2009.1110

Wu, Y., & Chen, T. (2016). An Up-to-Date Review on Cerebral Microbleeds. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* doi:10.1016/j.jstrokecerebrovasdis.2016.03.005

Yang, C. C., Tu, Y. K., Hua, M. S., & Huang, S. J. (2007). The association between the postconcussion symptoms and clinical outcomes for patients with mild traumatic brain injury. *J Trauma*, *62*(3), 657–663. doi:10.1097/01.ta.0000203577.68764.b8

Yuh, E. L., Cooper, S. R., Mukherjee, P., Yue, J. K., Lingsma, H. F., Gordon, W. A.,. . . Track-Tbi, I. (2014). Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: a TRACK-TBI study. *J Neurotrauma*, *31*(17), 1457–1477. doi:10.1089/neu.2013.3171

Yuh, E. L., Mukherjee, P., Lingsma, H. F., Yue, J. K., Ferguson, A. R., Gordon, W. A.,. . . Investigators, T.-T. (2013). Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. *Ann Neurol*, *73*(2), 224–235. doi:10.1002/ana.23783

Zhu, Y., Li, Z., Bai, L., Tao, Y., Sun, C., Li, M.,. . . Zhang, M. (2014). Loss of microstructural integrity in the limbic-subcortical networks for acute symptomatic traumatic brain injury. *Biomed Res Int*, *2014*, 548392. doi:10.1155/2014/548392

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